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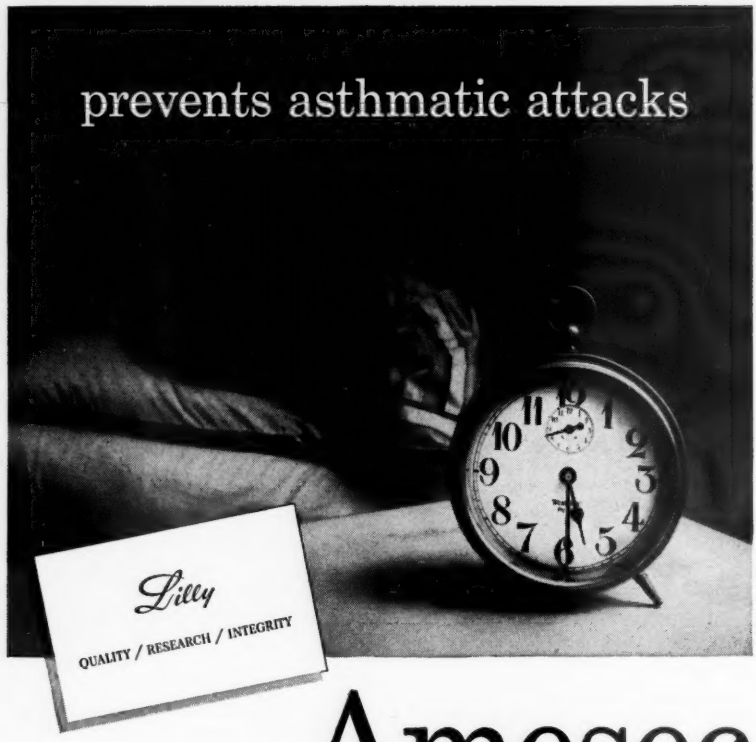

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ANNALS of ALLERGY

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BRONCHIAL ASTHMA CAUSED BY PSEUDOMONAS AERUGINOSA DIAGNOSED BY BRONCHOSCOPIC EXAMINATION

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INDIVIDUALS suffering from respiratory illnesses are often subjected to the prolonged use of antibiotic agents in an attempt to irradicate the causative organisms.[1] Since resistance to these antimicrobial drugs is increasing, organisms, usually harmless inhabitants of the body, have become dangerous pathogens. Numerous reports[5,8,9,10] in which pseudomonas have been discovered have included only one case of asthma.[9] A review of the literature since the original descriptions of 1917[6] reveals no case in which the organisms had to be obtained by bronchoscopy.[3]

CASE REPORT

A seven-year-old white female child was referred to our office on February 13, 1953, because of bronchial asthma.

Past History.—The onset of her wheezing was treated by the use of intramuscular injections of penicillin. For a time, these injections would clear the lungs; however, after a period of about ten days, coughing would recur, followed by wheezing.

Because of the severity of this condition, the patient was given a suppressive cough mixture and a course of oral penicillin. By the time she was seen by us, she had received, during a period of three months, aureomycin, terramycin, and streptomycin. Each new drug seemed to relieve the disorder for a short period of time.

Allergic History.—There was no childhood history of allergy, but there was a family history of allergy. The mother had hay fever each spring, and the father had a contact sensitivity to wool and was an inactive case of pulmonary tuberculosis. The family had acquired a dog about the time the child began to wheeze. The father raised parakeets in the backyard; however, it had been a year since any of these had been kept in the house. She had always used a feather pillow.

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Physical Examination.—The child was a well developed, chronically ill white girl with a typical pertussis-like cough. The temperature was 98.6° F, respiration 30, and the pulse rate 88. The nasal mucous membranes appeared to be injected and the inferior turbinates were swollen. The tonsils were slightly hypertrophied and the throat was hyperemic. The wheezing was heard throughout the entire chest; sonorous and sibilant râles were heard, markedly exaggerated by cough. The remainder of the physical examination was noncontributory.

Laboratory Examinations.—The red blood count was 3,800,000 per cubic millimeter, the hemaglobin 11 gm per 100 cc of blood with a differential count of 52 per cent neutrophils, 42 per cent lymphocytes, 1 per cent monocytes, and 5 per cent eosinophils. A sputum smear was negative for acid-fast bacilli and showed a few neutrophils, Gram-positive cocci, Gram-negative bacilli, and Gram-positive bacilli. Skin tests for coccidioidomycosis and histoplasmosis were negative. A complement-fixation test was negative for ornithosis, and no cold agglutinins or agglutinins for streptococcus M.G. were demonstrable. A nasal smear was negative for eosinophils and showed numerous neutrophils. The roentgenogram showed slight emphysema, but no evidence of an obstructing foreign body. Skin tests were performed and the patient was found to be mildly reactive to house dust, mesquite and mountain cedar.

Clinical Course.—She was started on a trial of hyposensitization on February 19, 1953, with house dust. Despite the use of aminophylline orally, potassium iodide and ephedrine sulfate, the patient continued to wheeze. Allergy management was continued without the use of antibiotics. Sputum and blood cultures previously taken were reported as negative. A Vollmer patch test was positive (four plus).

The patient was referred to a pediatrician, who, after complete examination and laboratory studies, concluded that the condition was a modified pertussis. The cough plates were negative.

On April 3, 1953, it was felt that the continued wheezing and croupy cough were due to a foreign body or bronchiectasis. The patient was admitted to the hospital and a bronchoscopy was done. This revealed pseudomonas aeruginosa on smear and later in pure cultures. The bronchogram was negative. Sensitivity studies revealed Chloromycetin® to be inhibitory. The lungs cleared some following the bronchoscopic aspiration, and a course of Chloromycetin Palmitate was started. Further sensitivity studies revealed polymyxin B (Aerosporin®) to be most inhibitory. This was administered in a dose of 2.5 mg per kilogram per day, for a period of eight days. The wheezing and croupy cough, altered by the first procedure, was completely eliminated. Subsequent nasopharyngeal studies have been negative. The patient was last seen on February 12, 1955, and has remained free of all asthmatic symptoms.

DISCUSSION

Pseudomonas aeruginosa is a normal inhabitant of the gastrointestinal tract. It is also found on the skin, in water, and in the air.[4] The presence of the organism in the air classifies it as an inhalant, which on entry into the lower respiratory tract can apparently cause increased secretions, edema and bronchospasm, resulting in asthma. This can occur in susceptible individuals who have had long courses of antibiotics and can be erroneously diagnosed as allergic bronchial asthma. Usually sputum and nasopharyngeal cultures reveal the organism. In this case, it is seen that the possibility of overlooking the specific organism, without the employment of bronchoscopic examinations, is very likely. Polymyxin B

(Aerosporin®)[7] has been reported to be the most effective antibiotic against these organisms. *In vitro* sensitivity studies, however, determine the choice of treatment.[7] Previous reports[2,10,11] of the toxicity of this drug have been recently reviewed. Cases of severe bronchial asthma which have been subjected to prolonged antimicrobial therapy, unimproved by allergy management, should be examined by bronchoscopy to establish a diagnosis, especially where sputums are negative.

SUMMARY

A case of severe bronchial asthma caused by pseudomonas aeruginosa in a seven-year-old white female child is presented. The possibility of inhalation of the organisms during or after the prolonged use of antibiotic drugs is presented. Bronchoscopic examination revealed the specific organisms causing the asthma, after sputum cultures had been found to be negative. The failure of the allergic hyposensitization to bring about relief prompted this type of diagnostic procedure, resulting in complete relief of the asthma, by the use of chloramphenicol and polymyxin B (Aerosporin®).

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OVERTREATMENT DERMATITIS

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IT is a daily event to see patients carrying so much medicine that they are confused about when to take it. Pill boxes are in vogue again, and some patients like to point out their various medicines and recite what each will do. Prescribing has reached the place where the side effects from one drug are to be offset by using another, and, perhaps, it will soon be popular to administer a third to do away with the bad effects of the first two. It appears today to be unpopular to believe that the human body has any defensive or healing attributes. A few remarkable so-called "wonder drugs" have fostered a tolerance and acceptance of many unremarkable ones.

Overtreatment is the use of too much medicine for any disease or its symptoms and its extent is reflected by the difficulty in finding the etiology in drug eruptions. Often so many remedies are mixed in the system that it takes weeks of eliminative study to detect the guilty one.[1] Finding the drug inducing a blood dyscrasia is sometimes impossible because so many were taken. A common aftermath are toxic sequelae which may not be recognized for a long time. Some risk is permissible in those diseases with a serious prognosis, but drug toxicity in self-limited disorders is another matter. Overtreatment is going to be challenged by the incidence of minor, severe or fatal drug reactions in trivial human ailments.

At a forum in 1939 on "Overtreatment in Dermatology" Miller et al[9] stated: "A comparatively large number of patients in dermatologic practice are forced to seek treatment because of irritation from remedies applied and not due to their primary complaints." Cutaneous medicine has always carried a heavy burden of things to do and compositions to apply, but this is the first time that dermatologic therapies had begun to produce a significant number of drug reactions. In 1938 manufacturers were straining to produce enough sulfonamides. These were urged for cutaneous application and are still in use for dandruff; however, the early enthusiasm soon turned to dismay. Next, penicillin came into use, and the topical sulfonamides were cast aside in ratio to the availability of topical antibiotics. Again, the first results proved misleading. All along, there was a wide use of the organomercurials for the prevention and treatment of skin infections. Topical anesthetics ("caine compounds") and antihistamines have had a therapeutic history on the skin like the sulfonamides, antibiotics and organomercurials. Overtreatment in dermatology furnished the precedent for introducing new drugs whose true pharmacology was determined by the incidence of side effects.

Dr. Gaul is an Associate Fellow of The American College of Allergists.

Presented at the Eleventh Annual Congress of The American College of Allergists, Chicago, Illinois, April 29, 1955.

INCIDENCE OF OVERTREATMENT DERMATITIS

In 1953 the late C. Guy Lane[10] determined from a group of dermatologists how many cases of overtreatment dermatitis they encountered in one month, and the average number reported was twelve. This approximates 140 cases per year, which, when multiplied by the number of practicing dermatologists, led Lane to conclude that at least 150,000 cases occurred annually. Pillsbury[11] believed that a figure of one million cases annually would be quite conservative. For a number of years the author has seen an average of twenty proved cases a month of contact dermatitis, overtreated in at least 35, and often 50, per cent of the patients.

The material for this report covers the number of cases of overtreatment dermatitis seen during the first quarter of 1955. An incidence of 13 per cent was found, and if drug eruptions from oral or parenteral administration were included this figure would reach 17 per cent. The number and distribution of cases appears in Table I.

TABLE I. NUMBER AND DISTRIBUTION OF DRUG DERMATOSES. FIRST QUARTER 1955.

New Cases	Old Cases	Overtreatment Dermatitis	Drug Eruptions	Grand Total of Cases
39	17	56	17	73

The diagnosis of overtreatment dermatitis was confirmed by means of past-treatment patch tests.[3] A case was considered new if there was no previous record in the files. The distribution in old cases compared to new cases confirms a suspicion that once a therapeutic sensitization occurs, repeated episodes of dermatitis are common. If this survey had been made during the rhus season, and if past experiences are any indication,[12] the total number of cases of overtreatment dermatitis would be tripled or quadrupled. If to these were added reactions of rhus antigen injections, the grand total of cases would be highly significant.

The number of drug dermatoses is seen from a different view by the data in Table II.

TABLE II. RATIO OF DRUG DERMATOSES TO OTHER SKIN DISEASES. FIRST QUARTER 1955.

Grand Total Drug Reactions	Acne Vulgaris	Hand Eczema	Atopic Dermatitis	Tinea Capitis
73	44	39	38	20

These figures arouse contemplation. Do they represent normal or average expectancies? Drugs are potent agents and produce good as well as bad effects. What shifting of the ratio is critical? If the incidence of accidents from the tools of our skill are compared to accident rates in factories, a stunning difference would be seen. Safety knowledge in industry may be compared to the tempo of drug advertising in our profession. Seven pa-

tients in this series had to be hospitalized, which is clear evidence that cutaneous reactions from medicines are far from trivial.

Past-treatment patch tests were done in ninety patients, and the ratio of responses and degree of positivity are shown in Table III.

TABLE III. RATIO AND DEGREE OF POSITIVITY FOR PAST-TREATMENT PATCH TESTS

Number of Cases Tested	Number of Plus Reactions	Degree of Positivity	
		1-2 plus	3-4 plus
90	56	19	37

Asking dermatologic patients to bring in the remedies they have used, and having them make a special effort to find those that have been mislaid or borrowed, produces a high ratio of positive patch tests, about 60 per cent. This ratio is far ahead of any other group of contactants ever tested, such as plant resins.[2,12] Testing should be delayed until acute manifestations of the dermatitis have subsided. Remedies producing one to two plus reactions were, for the most part, those whose ingredients included the essential oils, salicylic and benzoic acid. The responses were like those to soap solutions, a dull to bright erythema with moderate edema tending to persist for days to weeks.

Three to four plus reactions were produced by the organomercurials, antibiotics, "caine compounds" and antihistamines. The indications of these same agents in cutaneous medicine stand out in a most unfitting role compared to their test reactions. The first two, instead of favoring healing by obviating infection, seem to delay healing, and they produce such tissue damage that favorable soil is created in which infection may take place. Nevertheless, the last two have been widely acclaimed for dermatologic symptoms.

When past-treatment patch tests are being done with these four classes of topical therapeutic agents, it is a good plan to limit tests to the medicine the patient brings in. A severe reaction—massing of vesicles, bullae and flaring—to their own medicine is looked upon a little differently than if the preparation is taken from a testing tray.

A review of the directions and indications for proprietary skin remedies will reveal that the cutaneous lesions shown in Table IV correspond closely with those the public is considered able to treat properly. Vigorous treatment is given to injuries and environmental dermatoses,[5,7,8] and most proprietaries are indicated for eczema. Under contact dermatitis seventeen cases are listed. The diagnosis was wrong in all but two instances, both cases of rhus dermatitis. Even these two cases were treated with a local anesthetic and a topical antihistamine that induced therapeutic sensitization. The data in Table IV are a reminder that cutaneous lesions need skillful interpretation before treatment is instituted, especially if this consists of irritating and sensitizing drugs. In this series are nineteen

TABLE IV. CLASSES OF SKIN LESIONS AND TOPICAL REMEDIES PRODUCING OVERTREATMENT DERMATITIS

Skin Lesions	No. of Cases	Antiseptics	Antibiotics	Local Anesthetics	Antihistamines	Miscellaneous	Prescriptions
1. Injuries	8	merthiolate 6	Aureomycin 2				
2. Environmental Dermatoses	13						
Atopic dermatitis 6					Surfadil	Pragmatar D.D.D. Cuticura soap, ointment Blue Star Balm	1
Sunburn (lamps) 2		merthiolate 1					
Leg eczema 3		hexachlorophene 1		benzocaine (Topaminic)		D.D.D.	
Chapping 2		merthiolate 1 mercury salicylate 1 (soap-ointment)					
3. Ear eczema	6	merthiolate 4		benzocaine 1	Caladryl 1	Breck Balm 1	1
4. Occipital eczema	2					Chapping cream 1	1
5. Drug eruption	2		Terramycin Aureomycin			Wonder Salve	1
6. Seborrhea Dandruff Psoriasis	4	Zephiran 1 mercury salicylate 1				D.D.D.	1
7. Ano-genital dermatitis	3	mercury salicylate 1		Quotane 1 benzocaine 1			
8. Contact dermatitis	17						
Diagnosis treated:							
Fungus 7				Tronothane 2	Caladryl 2	Lifebuoy soap, Neko Black salve	1
Rhus 6		merthiolate		Calacreme	Pyribenzamine	Ivy Dry	
Food rash 2		sodium hypochloride		Surfacaine		Wonder Salve 2	
Scabies 1				benzocaine		Chapping cream 2 D.D.D.	1
Eczema 1				Quotane		Campho-Phenique	7
Total	55	19	2	10	5	20	14

cases with sensitivity to various antiseptics, two to antibiotics, ten to local anesthetics, and five to antihistamines.

An important aspect of the subject of overtreatment dermatitis is the tremendous number of topical drugs inducing therapeutic sensitization. Listed in the table under "Miscellaneous Proprietaries" are twenty different preparations producing various degrees of patch test positivity. Another important aspect of the subject is the fact that there are fourteen prescriptions whose composition is not known which alone or in combination with proprietaries and used topically had induced cutaneous sensitization. The tendency exists for the same cutaneous drugs to be sold over the counter as well as by prescription. Often the patient is using a proprietary, and the physician unknowingly will recommend in prescription form the same drug.[4,6]

Fig. 1. This is an example of the drug armamentarium lay therapists use for preventing and treating infections alleged to be present in trivial injuries. Seven different remedies were used in one week, or one remedy per day.

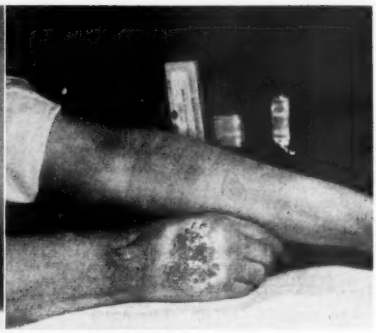

Fig. 2. Past-treatment patch test reactions are shown on the left forearm, pictured above the organomercurial sensitization dermatitis on the dorsum of the right hand.

INJURIES

Case 1.—E. C., an eighty-four-year-old retired minister, injured the right third finger while using a screw driver. The therapeutic agents in Figure 1 were applied during a period of one week, and the finger became swollen to twice its normal size. The scratched site showed a mass of pustules stained by medicines and surrounded by thick-walled vesicles. Deep-seated "ids" covered the hands, forearms, face and neck. A patch test with Merthiolate® produced in eight hours a bullous lesion with a halo of erythroedema, 8 centimeters in diameter.

Case 2.—H. T., a white drug salesman, aged fifty-nine, was seen for an eroded and blistered dermatitis affecting the dorsum of the right hand. The area had been scratched a week ago. Patches of vesicles covered the left hand, forearms, face, neck and feet. Merthiolate® had been used three times daily for five days when the infection "got ahead of him," so he called a physician. Neomycin® ointment was advised twice daily. It admixed with Merthiolate, but the spreading was thought to be due to the Neomycin. Patch tests proved the etiology of the sensitizer (Fig. 2). *Comment:* Mixing remedies always favors the development of overtreatment dermatitis.

ENVIRONMENTAL DERMATOSES

Case 3.—Atopic Dermatitis. L. F., a white female baby, was born December 29, 1954, and placed on a diet of breast milk. Skin care consisted of the daily use of soap, lotion and powder. On the eighth day of life, January 6, the air temperature reached 70° F., and the dew point 60° F. (Fig. 3). On January 10, the air temperature was 10° F., and the dew point 10° F. At these weather conditions, moisture is removed from the skin so rapidly that severe chapping results. On January 10 or 11, the mother noticed a rash on the right cheek. This set in motion something akin to a chain-type reaction. Soap and water was rubbed on to keep the area clean; a lotion was daubed on, and then a liberal amount of powder. On top of this, a salve was smeared. Then a relative decided that she had a salve that would work better.

On January 12, a physician was seen. Now the treatment chain reaction really began. Breast milk was stopped and Formula I started. Diapers were to be rinsed

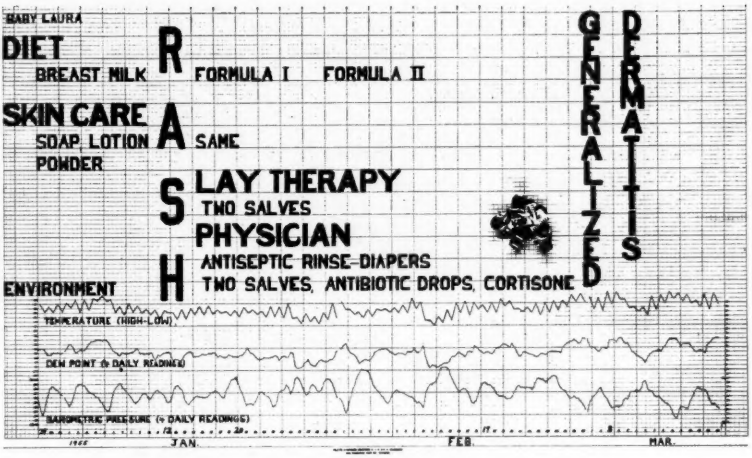

Fig. 3. Overtreatment in a baby. The diet was changed back to Carnation Milk and Karo Syrup, March 3. By March 15 the skin was improving rapidly. A mild seborrheic capitis still affected the frontal area of the scalp. It would seem that the environment shifting to circumstances favoring higher temperatures and higher dew points was instrumental in improving this baby.

in mercuric chloride solution, and, for good measure the other wrappings, too, were rinsed by the mother. A sample tube of salve was advised, and a few days later a different kind was tried. On January 20 the child was no better. Formula II was started, antibiotic drops were administered, and the use of the second salve was advised, but the mother thought this was not helping so she began to apply the first tube of salve again. All this time, the skin care—soap, lotion and powder—was going on as usual. By February 17 the treatment chain was consummating the reaction. The rash was now present over the entire head, neck, upper extremities and torso. Cortisone ointment was advised as well as an oral antihistamine (not shown in the illustration). The little tubes of ointment covered so little and cost so much that despair settled on the family and physician when recovery failed to appear. The treatment chain reacted faster, and by March 3 there erupted a generalized dermatitis. Dermatologic therapies established an unusual precedent; a rash on the left cheek under treatment spread to become a generalized dermatitis. *Comment:* Explanations come forth glibly to solve this case. It was stubborn; it did not respond; the infection was deep-seated; secondary infection developed. These excuses may be plausible and satisfying, but they do not circumvent the overtreatment sequence. This baby was restored to health by stopping treatments. There had been so much treatment that it was impossible to ascertain what was harming and what might be helping.

Case 4.—Chapping: M. K. is a white woman, aged thirty. Two days before admission she was doing some work in the yard, and on coming indoors noted that her face burned and felt dry. She immediately applied a hand cream. When there was no improvement within an hour or so, she applied Mazon® ointment, and that evening washed her face with Mazon soap. The next morning, she was unable to open her eyes. The severe erythrodermia is shown in Figure 4 although this photograph was taken after two days of conservative management to reduce the edema. Past-treatment

patch tests with Mazon ointment and Mazon soap produced vesicular responses. A series of metal tests performed simultaneously disclosed a positive test to mercuric chloride 0.1 per cent. *Comment:* This patient had a mercurial sensitivity existing prior to the chapping of the face. The history disclosed that after the last pregnancy, a faint rash developed where Merthiolate had contacted the skin. No doubt, Merthiolate initiated the mercury sensitivity, and the exposure to Mazon ointment and soap, containing mercury salicylate, induced the overtreatment dermatitis.

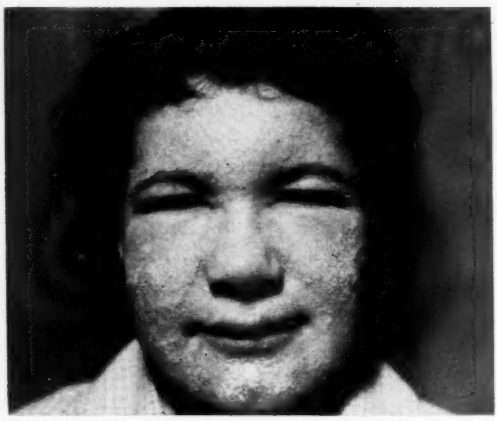

Fig. 4. Severe erythrodermia with marked edema of the eyelids due to sensitivity to an organomercurial.

EAR ECZEMA

Case 5.—J. H., a white girl, aged nine, saw the family physician for an earache in the right ear. Ear drops were prescribed, also an oral antibiotic. After four days of treatment, the child complained of itching of the right ear lobe. The physician was called, and a pink cream was recommended. The next day, both ears showed a bright erythema and the itching worsened. The mother then applied Caladryl®, which was a year old and had been used to relieve the itching of chicken pox in another child. Within hours the dermatitis spread to the face, neck and shoulders. Past-treatment patch tests were positive to the pink cream (composition unknown) and Caladryl. *Comment:* Patients and parents will often resort to self-treatment while under the care of physicians. In this case, the remedy advised by the physician and the one used by the parent were both sensitizers.

OCCIPITAL ECZEMA

Case 6.—L. J., a seventy-six-year-old white woman, was seen for an acute dermatitis affecting the face, neck, shoulders, hands and forearms. For a number of years, she had had a recurrent patch of dermatitis in the occipital region of the scalp. Several months ago a dermatitis developed on the left thigh, which was considered to be a fungus infection. The family doctor recommended the use of three different prescriptions. The last one used caused the eruption on the thigh to spread, and simultaneously a dermatitis appeared over the back of the neck, face, hands and forearms. The preparation used on the leg had also been used by the patient to treat the dermatitis on the back of the neck. Past-treatment patch tests disclosed a strong four-plus reaction to a pink lotion, composition not known. Subsequent investigational studies disclosed that this patient was reacting to tetramethyl-

thiuram monosulfide, a rubber compound. This information pointed to rubber as the source of the dermatitis. When she stopped wearing a hair net and stopped resting the rubber enema bag on the left thigh, the dermatitis underwent rapid involution. *Comment:* This case is an example of the need for investigational studies in dermatoses, and re-emphasizes the importance of diagnosis before treatment with known irritating and sensitizing drugs.

DRUG ERUPTION

Case 7.—D. B., a white girl, aged three, had never experienced any skin trouble, until December, 1954, when a diagnosis of ear infection was made and Terramycin® drops were recommended. These were taken for a period of four days, and the ear was said to be considerably better. A recurrence in January prompted further medication with the antibiotic. The following day a rash appeared around the waist with severe pruritus. The child was taken to another physician who called the condition scabies and recommended a white lotion. This produced considerable burning where it was applied. As more of the lotion was used, a patchy, erythematous dermatitis developed. The use of the lotion on the second day produced such extreme burning that the parents consulted another physician. A past-treatment patch test was positive to the lotion, composition unknown. *Comment:* This case illustrates the importance of using non-irritating preparations, such as milk of magnesia, bentonite lotion or Lassar's paste, until there is good evidence to support a specific diagnosis. There was no clinical or laboratory evidence that this child had scabies, nor were any other members of the family affected.

SEBORRHEIC DERMATITIS

Case 8.—F. M., a seventy-four-year-old white man, had a recurrent dermatitis affecting the scalp and face of twenty-five years' duration. Examination revealed an acute dermatitis affecting the face with marked edema of the eyelids and ears. Throughout the scalp were weeping and crusted patches. This patient was hospitalized for evaluation. The routine laboratory studies and a survey of the physical status by an internist disclosed no unusual findings. A series of patch tests was done, including one with a brownish liquid medicine that the patient had used off and on for many years to relieve dandruff. The tests produced negative results except for the brown medicine which produced a weeping patch with a surrounding flare about 6 centimeters in diameter. *Comment:* The medicine was a prescription and it was impossible to ascertain its composition. The history of its use coincided with the recurrent attacks of dermatitis. In spite of the positive patch test and the prompt involution of the dermatitis when the medicine was stopped, this elderly patient still believed that it was the best dandruff preparation he ever used.

ANO-GENITAL PRURITUS

Case 9.—C. S., a white woman, aged seventy-two, had never had any dermatitis until the first part of February, 1955. In December, 1954, she had what was considered to be pleurisy and was given an antibiotic. Several weeks later, a rash appeared on the vulva which was associated with considerable burning on urination. Three or four different home remedies were used to relieve the burning, and in early January she consulted the family physician. Two different kinds of salve were recommended, and when there was no improvement, cortisone ointment was advised. Four tubes were used without sufficient improvement to justify its expense. About this time a friend of hers in a different city, who had learned of her difficulty through a relative, sent her a tube of Quotane® ointment. This was used for about four days. Intense and uncontrollable pruritus developed, followed by a weeping dermatitis of the vulva and perianal region, and the appearance of vesicular patches over the torso, arms and thighs. She was hospitalized, and during

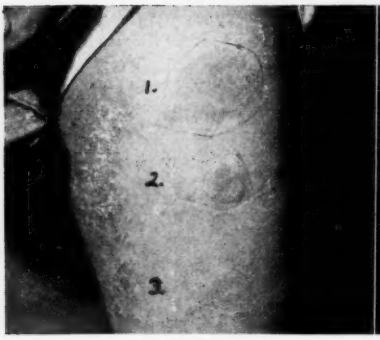

Fig. 5. Patch test reactions: (1) New Lifebuoy soap 1 per cent (tetramethylthiuram monosulfide). (2) Old Lifebuoy soap 5 per cent. (3) Neko soap 1 per cent solution.

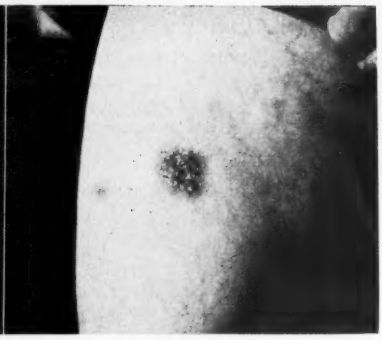

Fig. 6. Bullous patch test reaction to Ivy Dry.

the course of investigations a diabetes mellitus was discovered by means of a glucose tolerance test. Two previous urinalyses had been negative. *Comment:* All cases of ano-genital pruritus, especially when persisting a month or more, should have a post-prandial blood sugar determination.

CONTACT DERMATITIS

Case 10.—L. V., a forty-three-year-old white man, was seen for an acute erythrodermia affecting the face, ears, neck, arms, thighs and legs. The dermatitis had appeared following washing with a new deodorant soap, Lifebuoy. Three salves had been used to treat the dermatitis, but instead of improving it had tended to become worse. Patch tests were performed with a series of metals and four rubber antioxidants. A vesicular reaction was obtained to tetramethylthiuram monosulfide, also a similar reaction to mercuric chloride 0.1 per cent. It then was recalled that the new Lifebuoy contained this chemical as a deodorant. Patch tests were performed with the new Lifebuoy soap 1 per cent and the old Lifebuoy soap 5 per cent. The positive responses are shown in Figure 5. At the time of the onset of the dermatitis, this patient had purchased a bar of Neko soap which proved an additional aggravating factor because of its mercury content. *Comment:* This is an example of sensitization to a rubber chemical, in which an acute dermatitis developed from an exposure to the same chemical via a different source, namely soap. The therapeutic agents used by the patient as well as the physician proved to be sensitizing therapeutics, which explains the generalized dermatitis. Routine investigations disclosed this man also had a mild diabetes.

Case 11.—G. P., a white man, aged fifty-seven, was referred for a weeping erythroedema affecting principally the arms, face and neck. He was hospitalized. Three weeks previous he had noticed a rash on the left forearm, which was considered to be poison ivy. A lotion was prescribed, and a course of six injections was given to effect relief of the symptoms and heal the rash on the wrist. Instead, the rash began to spread, the erythema deepened, and marked edema appeared, followed by weeping. At this stage, a brownish lotion was applied, and within a matter of hours, a generalized dermatitis developed. Past-treatment patch tests disclosed a marked sensitivity to mercury (0.1 per cent mercuric chloride) and the brownish

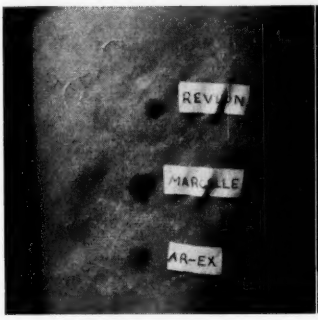

Fig. 7. Reactions of similar intensity to three brands of nail polish.

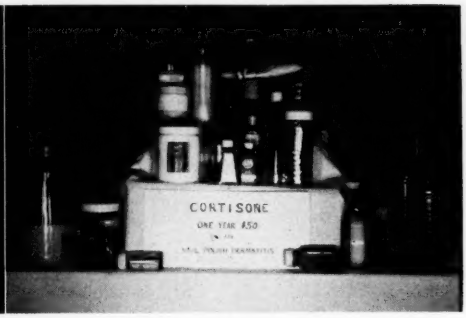

Fig. 8. Information noteworthy for its conclusiveness has been disseminated about the value of the corticosteroids in contact dermatitis. This has led to their wide usage and apparently has tended to shift importance to them instead of adequate diagnostic study.

liquid (Fig. 6). It was learned later that this was Ivy Dry. *Comment:* Rhus antigens for treatment and relief of symptoms of poison ivy are still in wide use. Reactions from this procedure make up a good proportion of the drug dermatoses in rhus dermatitis.

Case 12.—L. R., a white woman, aged fifty-five, had a persisting dermatitis on the chin, neck and ears for a period of one year. On several occasions, it had almost disappeared, only to recur. The clinical diagnosis was a food rash, and for a year this patient had been on various diets, but there was no lasting improvement of the dermatitis. Patch test investigations showed a marked sensitivity to three brands of nail polish, also a hand cream which had been used to treat the dermatitis, and a stick cologne that had been used in back of the ears. When this patient saw the patch test reactions (Fig. 7) to the nail polish, she could not reconcile the reactions to the fact that she had been told that this nail polish was nonallergic. *Comment:* Information reaching the public about the skin and the actions and uses of various cosmetics, soaps and chapping creams seems to be accepted as factual information, and in many instances, this is the basis of failure of treatment in some patients.

Case 13.—H. B., a white woman, aged thirty-eight, developed a rash on the left hand during the summer of 1953. This was called a fungus infection and a variety of fungicides were used. Before long, the skill of four general practitioners was exhausted, and she then came under the care at various times of four dermatologists. In spite of diligent efforts to effect a resolution, the eruption continued to remain chronic with marked symptoms. When observed, there was present a weeping eczematization of the neck, ears, both hands and forearms, axillae, infra-mammary regions, pubic, perianal region and thighs. Under this lady's bed was almost a bushel of remedies that had been tried in the therapy of the dermatitis. A series of patch tests was performed, and she was found sensitive to chromate, 1 per cent solution, and, in addition, four therapeutic agents which had been in recent use on her skin. These are shown in Figure 9. This lady was discharged from the hospital at the end of two weeks with the skin in fairly good condition, except the right hand. The use of some home remedy produced another exacerbation and she was

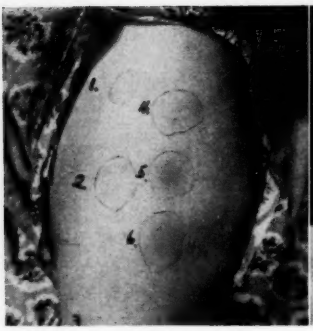

Fig. 9. Patch test reactions: (1) Caladryl. (2) Tronothane. (3) Quotane (not in focus). (4) Potassium chromate 1 per cent. (5) Surfacaine. (6) Metacaine.

Fig. 10. This shows the medications that were used over a period of eight weeks to relieve pruritus, the therapy of which produced a generalized dermatitis. The oat wash on the right had fermented, but the patient was convinced that this did not interfere with its helpfulness for his condition.

re-hospitalized for another period of two weeks. *Comment:* This experience emphasizes the need for early diagnosis in dermatologic patients and the hazards of using irritating and sensitizing drugs and steroids until such a diagnosis is made.

Case 14.—J. G., a fifty-two-year-old white laborer, noted an itching of the neck one evening after being exposed to cement dust. A wool collar seemed to aggravate the itching. He scrubbed his neck with Synol® soap because of its antiseptic properties, and then applied Campho-Phenique® liberally. During a period of three weeks, he used eighteen bottles of Campho-Phenique and three bars of Synol soap. The initial itching of the neck was now the site of a brightly erythematous dermatitis, and about this time, someone told him about the value of whiskey and camphor. This was prepared according to directions from his friend, and this, too, was applied to the skin. Over the next two or three weeks, the dermatitis steadily spread, so that after six weeks of home treatment (Fig. 10) he had developed an erythrodermia. When the acute phases had subsided, past-treatment patch tests were performed. The Synol soap and Campho-Phenique produced strongly irritative reactions, as did the whiskey and camphor. Diagnostic patch tests revealed a sensitivity to potassium chromate. *Comment:* This example is convincing evidence that the public does not appreciate the significance of cutaneous symptoms, nor are they concerned about the nature of dermatologic signs, but regard themselves as proficient when it comes to applying drugs to the skin. Lay therapists in dermatology have depraved the meaning of the word, treatment.

SUMMARY

The comment is heard that self-treatment of skin disease is a time-honored right of people and no one should question this prerogative. This is not denied, but there is a difference now compared to several decades ago. People could daub themselves to their heart's content with calamine lotion or Lassar's paste and the chances for harm would be unlikely, only the diagnosis would be delayed. Today, however, remedies in their hands

are of different composition. Powerful therapeutic sensitizers have replaced former innocuous ingredients. People are unaware of this. Advertising of skin remedies has broadened to extoll publicly the claims for the new and supposedly better formulas. Knowledge about their use and what to use them for has not changed. It is still enshrouded by the calamine lotion days. The use of antiseptics, germicides and disinfectants on the skin represents one of the strangest paradoxes in modern dermatological therapy. An imagined state of possible disease unless an antiseptic is applied becomes transformed into a real disease by the development of a therapeutic dermatitis.

Overtreatment dermatitis during the first quarter of 1955 was the single most prevalent skin disease observed. Physicians should try to restrict their treatment to a relatively small number of therapeutic agents with a low sensitizing index, and they should suggest pretreatment patch tests with any ointment likely to be a sensitizer.

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IS THERE A SPECIFIC EMOTIONAL PATTERN IN ALLERGIC DISEASE?

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THE effect of emotions on the physiologic processes of the human body is as old as the reading of the stars. Hippocrates[7] alluded to it when he wrote, "Fear, shame, pleasure, passion . . . to each of these the appropriate member of the body responds by its actions," and for long centuries thereafter references constantly appeared linking mental excitement to disease. In the early dawn of medicine, in view of their crude and primitive knowledge of science, it is not surprising that agitation of the passions or sensibilities often was indicted as the malignant cause rather than as an accompanying evil symptom or as, in reality, an effect of the illness *per se.* Even today differentiation and distinction between cause and effect is not always crystal clear.

I

In recent years Wolfe and his co-workers[16] have demonstrated, to their own satisfaction at any rate, that symbolic words or descriptive events, which threaten the security of the individual by reason of earlier conditioning experiences, may initiate pathophysiologic reactions and lead to structural organic disease. According to these investigators, edema of the nasal mucous membrane, hypersecretion of mucus, and obstruction of the nasal passages with cellular and structural changes are identical with the symptoms produced by nasal pollen sensitivity. Miller and Baruch[10] have reported large series of children in whose lives there is a disturbance in the normal parent-child relationship. They consider this emotional disturbance, namely, maternal rejection, to be of the utmost significance in the production of allergic symptoms in children possessing an allergic constitution.

Culling psychiatric literature one finds numerous other allusions to the emotional component in allergic disease. Psychosomatic medicine in this instance appears to be on the filmy fringe of allergy. Thus we find Wilson[15] conceiving of hay fever to be the result of inadequately repressed olfactory sexual impulses; Saul,[12] using the language of the psychoanalyst, suggesting that hay fever and allergy in general, as well as colds, are manifestations of suffered intensification and frustration of passive receptive wishes with a strong oral component; French and Alexander,[4] leaning toward insecurity as the psychosomatic cause of asthma in children, likening the asthmatic wheeze to a stifled cry precipitated by threatened loss in security; Fromm-Reichmann[5] suggesting that migraine headache is due to repressed hostility toward loved ones in which the patient during childhood was frustrated in intellectual rivalry with a sibling or siblings;

Alvarez[1] claiming giant hives are caused by painful emotion and conflict, such as job loss, extreme anger, frustration in love, and examination difficulties. In a recent psychotherapeutic study of thirty-five patients with facial dermatoses of various kinds, including light sensitivity, permanent erythema, angioneurotic edema, urticaria and Besnier's prurigo, Macalpine[8] suggests suppressed anger as the emotion usually responsible for the lesions. According to Macalpine, in many cases the patients, "sensitized" to situations causing anger but being no longer aware of the emotion itself, found vicarious expression in the cutaneous lesion. "Depression," she says, "is merely anger no longer directed at the outer world but actually turned against self which is felt to be worthless," and depression was dominant in all her patients.

Current medical literature continues to abound in similar references. The foregoing were selected because the investigators are prominent in their field and their observations cover a variety of allergic diseases as well as a variety of emotional states. From their testimony there seems little doubt that emotional factors play a role in allergic disease. The question arises to what extent, in what manner, and whether or not any specific emotional pattern exists.

II

In considering the importance emotions play in allergic disease one must realize that many patients tend to dramatize their symptoms and emphasize the emotional aspects. Often they are confident and convinced in their own mind that their illness is due entirely to what they like to call "nerves." One must not condemn the patient who seeks to validate his nonmedical diagnosis of the etiology of allergic disease as one of emotional or psychosomatic origin. It was not so long ago that in days of illness patients turned to the supernatural as a cause of their discomfort. It was there they sought an explanation of the pressing phenomenon of disease. Even today over vast regions of the earth, magic, amulets, charms and incantations still are invoked, and many millions seek their gods rather than the physician for relief. To the ordinary nonmedical mind there is something mysterious about sickness, and allergy in particular. It is but natural that believing in superhuman agencies, which they could not see, as the cause of disease, the untrained mind should grasp upon emotional influences which it can recognize and feel.

Therefore, it is not uncommon for patients to frequently volunteer such information as, "it wasn't until [such and such a thing] happened that I noticed I couldn't breathe," or, "I never itched until [this and that] occurred; then I started scratching," et cetera. Studying psychologists' reports, one is struck with the number of times such statements by patients are eagerly grasped by psychologists as bona fide proof that the train of events happened *just that way*. It would even seem that some psychologists encourage such allegations. Whether or not that be true,

it certainly *is* true that when symptoms follow an emotional upset psychologists are prone to point to the allergist and rest their case with "there you are!" If, as frequently transpires, a remission occurs after a period of months, during which the patient may have undergone psychotherapy, the case is then definitely closed as asthma, neurodermatitis, allergic rhinitis, or whatever the diagnosis may have been, due to psychological upset, emotional disturbance, maternal rejection, sibling rivalry, fear, anger, frustration or tension. The research scientist checks and rechecks again and again to be sure of his findings; the clinical allergist is guided by Cooke's Postulates and other criteria before he draws his conclusions; the psychologist delving into allergic disease all too often readily accepts the patient's statement of circumstances, a parent's report or a friend's account as an observation, authentic, accurate and scientifically reliable. I am persuaded that seldom are they not serenely content and rarely do they delve further for corroboration or contradiction.

In the second place, one must recognize the pertinent fact that exact and definitive etiology of allergic disease is frequently obscure, and there is a distinct tendency, when etiology is unknown or difficult to determine, to classify the illness as due to a nervous influence. Side by side, for example, as substance and shadow, we know that before the advent of roentgenography, improved methods of serology, tests for liver function and the like, the diagnosis of "nervous stomach" was not uncommon. Today we know many of these so-called "nervous stomachs" were gastric or duodenal ulcers, carcinomas, diseases of the biliary tract or diseases of the liver. It is remarkable that Osler in *Principles and Practice of Medicine* maintained the term "neurotic" in discussing bronchial asthma until as late as 1935. It was not until the twelfth edition of his work was published that the term was deleted. All of this does not mean that emotions, personality problems, or nervous influences may not be a factor in disease. Undoubtedly they are.

The point is made, however, that as our knowledge of disease progresses and methods of investigation improve, as we learn more about immunochemistry, nuclear physics, and as our diagnostic intellect becomes more able to cope with them, it is probable the neuropsychiatric factor will assume its proper place in the etiology of allergic disease. At the present time, we concede there is no separation between psyche, the mind, and soma, the body, and that psychosomatic influences aggravate and, in some instances, precipitate a rare allergic reaction.

III

In a previous paper Shure and I[13] speculated on the several mechanisms which may properly explain this inter-relationship of mental and organic control of allergic disease. One is the thought that the allergic response is, at times, in the nature of a conditioned reflex. Anaphylactic reactions based on a conditioned reflex have been produced in animals. Metalnikov[9]

sensitized rabbits with cholera organisms and produced nonfatal anaphylactic reactions by subsequent injections of the cholera vibrion. Each injection was invariably accompanied by the beating of a gong, and it was possible eventually to elicit the expected allergic reaction merely by the sound of the gong. An attack of asthma may easily be initiated with an association of ideas conditioned by previous attacks.

Another possible explanation for the mechanism of an allergic response aided by emotional factors is that psychic influences may condition the autonomic nervous system in such a manner that excitants previously unable to produce reactions can now penetrate the barrier removed by the new threshold and cause an allergic response. When it is remembered that the respiratory tract, from its anatomic position and embryologic origin, is closely connected with the gastrointestinal tract, and that, furthermore, both are largely controlled by the autonomic nervous system, it is readily apparent that just as psychic influences, such as fear, love, anger and hate, affect digestion, they also may play a part in the production of dyspnea, orthopnea, chronic cough and edema of the nasal and bronchial mucous membrane.

It is entirely possible that emotional upheavals may influence the allergic state by way of the vascular mechanism. The relationship between the cortex and the thalamic area is well known. The thalamus is the great emotional center of the brain and, by its connections to the hypothalamus, influences the autonomic nervous system. Thus, emotional impulses from the higher centers of the brain may increase, by way of the autonomic nervous system, the permeability of blood vessels and allow the penetration of allergens previously held back by the vascular barrier; or by increasing the blood supply to a susceptible shock tissue or organ, they may aid indirectly the union of the circulating antigen with the sessile antibody.

It must be emphasized that, at our present state of knowledge, the fundamental etiology of allergic disease is organic, resulting from pollens, environmental antigens, food, fungi, and infection. There is no purely emotional allergic disease. The individual attack of asthma or hay fever, for example, may possess a high degree of emotional components, but the person must be allergic, in the organic sense, basically.

The question now arises about the effect of organic disease on the psyche. In prolonged illnesses, this has long been recognized. In allergy, an attack of asthma, with its terrifying sense of suffocation, is a frightening experience. An asthmatic patient, who has to look forward to these repeated attacks of suffocation with their attendant feeling of helplessness, is likely to be grouchy, irritable, quarrelsome, and apprehensive between attacks. During an attack this anxiety, aggravated by the situation, often has the tendency of perpetuating the seizure, thereby producing a vicious cycle.

The suggestion that a mother's rejection of her child is the cause of bronchial asthma has been questioned by Rogerson, Hardcastle and

Duguid,[11] who ask whether the intense need of children with bronchial asthma for mother's love is one of the causes of their asthmatic attacks or a result of them. There is room for argument that acute dependence on the love of a mother might result from the asthmatic symptoms themselves. Even French[3] recognizes this when he writes, "What wonder that a child who is constantly threatened with the danger of suffocation, and whose activity must be limited for fear of bringing on an attack, should feel the need always to have near him a mother to whom he can cling?" There is, accordingly, every reason to expect that the asthma attacks themselves should induce just the sort of helpless dependence that has been found to be characteristic of the deeper emotional life of our asthma patients. May not the personality traits that we have been describing be merely a secondary reaction to the disease itself?"

In a discussion of Macalpine's psychiatric observations of allergic and other dermatologic eruptions involving principally the face, Sulzberger and Baer[14] have this piquant comment, "In eruptions with an often unpredictable course like light sensitivity eruptions, urticaria, angioneurotic edema and atopic dermatitis, the evaluation of psychotherapeutic procedures is fraught with many possibilities of error. Over a period of many weeks (ten to twenty sessions) many 'spontaneous' fluctuations in the course of the eruption may occur, and especially in view of the relapses described by Macalpine, the therapist may be misled as to the efficacy of the treatment instituted. In many years of dermatologic practice, we have failed to see any patients who became depressed when their facial dermatoses cleared under purely dermatologic therapy. The question therefore arises whether the depressions noted by Macalpine were not due to the psychotherapy!"

IV

Is there a specific emotional pattern in allergic disease? The one which within these past few years has catapulted itself into the ranks of first place, especially in bronchial asthma of children, is the mother rejection theory, of which Miller and Baruch and French and Alexander have been the chief proponents. The conclusion of French and Alexander may be disposed of quickly, since all the cases studied were *allergic* asthma. That these cases showed mother dependency may have been, as French himself asserted, a result rather than the cause of the asthma, or, as Ziskind[17] so aptly states, "The psychologic factors uncovered might have been responsible for the concomitant neurotic symptoms and not related etiologically to the asthma at all. If one found cancer in a patient with long-standing psychasthenia, he would not attribute the tumor to the basic psychic conflicts. Even should over-dependency with a need for maternal love and protection represent a predisposing factor in all asthma syndromes without any independent psychiatric disease, the data would still merely point to a contributory or secondary psychologic cause." Ziskind also rejects Miller

and Baruch's findings with the succinct statement that "the almost 100 per cent incidence of rejection in the study of Miller and Baruch suffices to arouse one's skepticism, since such a well-nigh complete validation is rarely, if ever, found in clinical statistical studies. Such high figures suggest the possibility of the universality of rejection . . . we have all been accepted and rejected by our parents at different times." Theorizing still further it would seem that, if maternal rejection were an important cause of bronchial asthma in children, the juvenile homes of the country, where children who certainly have been rejected are placed, would be flooded with asthmatics. This certainly is not the case in San Francisco. Last year (1954), 6,986 children came under the jurisdiction of the San Francisco Youth Guidance Center (Juvenile Hall) and were examined in the medical department. These children ranged from two months to eighteen years of age.' Of the 6,986 seen, but five cases of bronchial asthma were diagnosed: two boys and three girls. This roughly is .06 of 1 per cent. So far this year (January 1 to March 28, 1955) 1,184 children have been reported ill, and only two with bronchial asthma!

But all psychologists do not agree that maternal rejection is the specific emotional factor causing bronchial asthma in children. Gillespie[6] states that asthma occurs as the accumulation of an anxiety, as expressing an emotional conflict, as a means of escape and as a conditioned response. He adds, "we find that almost every conceivable type of relationship between psychological factors and asthmatic attacks can be demonstrated by taking a sufficient number of asthmatic patients into consideration." Clarkson[2] summarized his observations on the nervous factor in 187 patients with ages ranging from two to twenty years. He found that the psychologic elements intruded in almost every case but that it was rarely the sole cause. "In 98 per cent of my cases," he writes, "I have not been able to demonstrate a purely psychologic cause for the onset of asthma in the absence of other causes."

In urticaria, all sorts of explanations emanate from the psychologists. "A feeling of guilt," someone says. "Sexual conflicts," says another. "Extreme anger, a wish to be ill, anxiety, frustration in business, frustration in love, sibling rivalry"—all these and many more are advanced as the specific emotional cause of hives. Obviously, they cannot all be the *specific* emotional pattern producing the disease. In neurodermatitis, a similar confusing situation exists with an equal number of emotional attitudes and patterns indicated as the cause.

The growing field of emotional experiences is vast in the complexities of modern life. Our attitudes are constantly altering with changes in discrimination, apprehension and understanding. Complex life situations in a world where nothing seems certain any longer are responsible for tensions that in certain individuals are more marked than in others, and in no two individuals necessarily the same. Like the body of Osiris, we are constantly being torn into a number of moods. Any or all may influence allergic dis-

ease, as indeed they may influence the progress of a patient suffering from any other type of illness.

V

Psychotherapy is a valuable adjunct in allergic therapy, but it should not be used as a curative measure to the neglect of the actual etiologic factor which is organic. It would be cruel to deny the patient the relief he might obtain from an allergic investigation, immunization and medication, by focusing his attention only on the emotional factors in his illness. There is no specific emotional pattern in allergic disease that has been convincingly proved.

Beckman in the opening sentence of his chapter on allergy in *Pharmacology in Clinical Practice* says, "You will probably observe, as I have, that allergists are an apprehensive group. This is not surprising since their preferred immunologic approach is constantly being assailed by such brash fellows as psychiatrists, endocrinologists and pharmacologists." Allergists admittedly need the pharmacologists; the endocrinologists confess that, except in cases of hormonal imbalance and with exception of the steroid hormones, the endocrines in allergy have proven essentially valueless; the psychiatrists are still with us. Allergists want them and need them, if for no other reason than to walk by their side and to comfort them! The allergist will, of course, continue to search for more exacting etiological diagnostic aids. There remains the spark, the gleam, which is the allergist's hope! However, no physician should neglect the emotional component in disease. To that end the allergist needs the psychologist and his therapeutic approach as an assist. In this way the specialty of allergy marches with time and continues to keep pace with medical progress in all its branches.

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SIXTH INTERNATIONAL CONGRESS OF OTOLARYNGOLOGY

The Sixth International Congress of Otolaryngology will be held in Washington, D. C., May 5 to 10, 1957. The subjects selected for the three plenary sessions are: Chronic Suppuration of the Temporal Bone, Collagen Disorders of the Respiratory Tract, and Papilloma of the Larynx. Outstanding internationally recognized authorities will open the discussion of each of these subjects.

Two types of communications are invited: Contributions to the discussions of the selected subjects, limited to five minutes, and original papers, limited to fifteen minutes. These should be in one of the four official languages of the congress: English, French, German, and Spanish.

Further information regarding this meeting may be obtained from the General Secretary, Paul H. Holinger, M.D., 700 North Michigan Avenue, Chicago 11, Illinois.

NEW YORK ALLERGY SOCIETY

At the annual business meeting of The New York Allergy Society, the following officers were elected for the year 1955-1956: President, Murray M. Albert, M.D.; President-elect, Samuel J. Prigal, M.D.; Vice President, Leoni N. Claman, M.D.; Secretary, Aaron D. Spielman, M.D.; and Treasurer, Joseph H. Fries, M.D.

HOUSE DUST ALLERGY

I. Occurrence of Seasonal Patterns of Asthma and Rhinitis During the Warmer Months of the Year

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IT is generally[1-6,8] believed at the present time that seasonal manifestations or exacerbations of respiratory symptoms in patients sensitive to house dust take place only during the winter or colder months of the year. While this opinion would appear to hold true in the majority of instances, it will be shown herein that at times one may encounter individuals who are exceptions, in that they undergo a season of symptoms during the warmer part of the year rather than during the colder part.

TABLE I. SUMMARY OF REPORTED CASES

	Age	Sex	Symptoms	Pattern of Symptoms
1. J.G.	19	F	Rhinitis and asthma	Perennial but worse in warm weather from spring to fall
2. G.M.	14	M	Rhinitis	Perennial but worse in spring (March, April, May)
3. G.L.	20	M	Rhinitis	Seasonal only in July, August, and September
4. R.Z.	40	F	Asthma	Perennial but worse in September and October

Table I gives the salient features of some cases that illustrate this point. Additional cases are available for citation, but because of limitation of space these four have been selected as being representative. They suffice to show, as does the larger series, that for some patients a "house dust season" may comprise all of the period of warm weather from spring to fall—which is exactly the reverse of the usual pattern—whereas for others the season may be much shorter and take place at different times for different patients (in overlapping or staggered fashion) throughout the warm period. This distribution of the clinical seasons throughout the warmer months can be shown to take place regardless of whether the symptoms are strictly seasonal, as in Case 3, or engrafted on a perennial basis, as in Cases 1, 2, and 4.

CASE REPORTS

Case 1.—J. G., a girl, aged nineteen, was first seen on September 10, 1948. Frequent paroxysmal sneezing and nasal blocking had been present since childhood. Symptoms were definitely aggravated in warm weather and in the two preceding months (July and August) had become unusually severe. Asthma had also been present for some years but was mild and infrequent until about ten days prior to the first office visit. Since then she had had daily wheezing severe enough to interfere with sleeping.

Scratch tests showed a few 1 + and 2 + reactions to diverse pollens and foods, and a 4+ whealing reaction to 1:200 Endo house dust extract. Intradermal tests showed

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a similar 4+ reaction to dust in both the 1:1,000 and 1:10,000 dilutions, and a few scattered 1+, 2+, and even 3+ reactions to various other substances not correlated with the reactions obtained on scratch test. None of the reactions other than that produced by house dust could be related to her symptoms by trial exposure to, or removal of, the non-pollen antigens. She knew that dust made her sneeze. Conjunctival tests with dry tree, grass, and weed pollens were negative.

Treatment with house dust extract was started the latter part of September, and the dosage was increased rapidly. On October 6, 1948, an injection of .77 cc of 1:500 Endo house dust extract produced an attack of asthma within fifteen minutes, requiring hypodermic administration of adrenalin for relief, and at the site of the injection the arm was swollen for an eighteen-hour period. Repetition of the same dosage and subsequent small increments of dosage produced repeated swellings and itching at the sites of injection, until finally a second systemic reaction of wheezing dyspnea occurred shortly after injection of .94 cc of the 1:500 dilution. The dosage was thereafter dropped to .70 cc of the 1:500 dilution, and no further attempt was made to go beyond this point. Perennial treatment was maintained for the next five years until December, 1953, during which time nasal symptoms were satisfactorily controlled and there was no recurrence of asthma.

Case 2.—G. M., a fourteen-year-old boy, had suffered from sneezing spells and rhinorrhea which began in New York in the spring of 1942. Symptoms persisted perennially from then on, but were always worse each spring. From July, 1948, to June, 1950, he lived in Washington, D. C., where the same pattern of perennial symptoms with seasonal exacerbation in spring was experienced. He came to Los Angeles in July 1950, and sought treatment in September. Skin tests to the usual variety of antigens were negative except for a 2+ scratch reaction to 1:200 Endo house dust extract and a 4+ intradermal reaction to the 1:1,000 dilution. Conjunctival tests to spring pollens were also negative, and treatment with house dust extract was therefore started. By the middle of October his nose had cleared, and he continued well until the middle of March, 1951. From then on until the end of May he had occasional mild spells of sneezing and nasal blocking, but the improvement in comparison to previous years was marked. In June the nasal symptoms again disappeared, and he remained well on continued therapy up to the time the family left Los Angeles in March of 1952.

Case 3.—G. L., a man, aged twenty, was first seen on September 1, 1950. He had had occasional mild asthma associated with chest colds since childhood. During the previous few years, he had noted nasal symptoms in July, August, and September of each year, but had experienced no nasal difficulty the rest of the year. His skin was nondermographic, and skin tests were negative save for a 4+ intradermal reaction to 1:1,000 Endo house dust extract, and a 2+ reaction to a 1:1,000 dilution of Bermuda grass pollen extract which did not explain the clinical picture. Injections of house dust extract were initiated. By the middle of September symptoms had disappeared, but this may have been due to the termination of his season. In October he began to notice some wheezing starting shortly after the injections. He failed to mention this and after three successive mild reactions he underwent a very severe reaction from an injection of .80 cc of the 1:1,000 dilution. Dosage was subsequently lowered and he experienced no trouble during July, August, and September of 1951. In November, treatment was stopped, and he stayed well during all of 1952. In July of 1953 both asthma and rhinitis recurred so that he returned again for treatment. Symptoms were controlled after a few injections, and he has since continued on treatment with no further outbreak of symptoms.

TABLE II.

Time (p.m.)	Procedure	Vital Capacity Readings in c.c.	Symptoms and Physical Findings
12:35	At rest	2800, 2800, 2800	Breathing comfortably, chest clear
12:40	10 inhalations of normal saline containing 0.5% phenol		
1:00		2800, 2700, 2800	Breathing comfortably, chest clear
1:05	10 inhalations as above		
1:25	10 inhalations as above		
1:30		2700, 2800, 2800	Breathing comfortably, chest clear
2:15		2800, 2800, 2700	Breathing comfortably, chest clear
3:40		2800, 2800, 2800	Breathing comfortably, chest clear
3:45	10 inhalations of 1:200 Endo house dust extract		
3:50		1900, 1900, 1800	Much wheezing, coughing
3:55		1800, 1900, 1800	Much wheezing, coughing
3:57	5 inhalations of 1:100 adrenalin		
4:00		2600, 2600, 2600	Slight wheezing still present, but breathing much more easily
4:10		2600, 2600, 2600	Chest slightly "heavy" but feels comfortable
4:30	5 inhalations of 1:500 Endo house dust extract		
4:35		2200, 2200, 2200	Again wheezing and coughing
4:40	5 inhalations of 1:500 Endo house dust extract		Still wheezing
4:45	5 inhalations of 1:500 Endo house dust extract		Wheezing
5:00		2200, 2200, 2200	Wheezing, complains of difficulty in breathing
5:10		2400, 2400, 2400	Chest symptoms less severe than ten minutes ago
5:35		2800, 2800, 2800	Breathing comfortably
5:36	10 inhalations of 1:500 Endo house dust extract		
5:45		2200, 2300, 2200	Wheezing
6:00		2200, 2200, 2200	Wheezing
6:15		2300, 2400, 2400	Wheezing
6:16	10 inhalations of 1:100 adrenalin		
6:25		2700, 2800, 2800	Chest almost clear except for a few sibilant rales on forced expiration

Case 4.—R. Z., a forty-year-old woman, was first seen in November, 1950. Asthma had set in about twelve years previously and was mild and infrequent until the fall of 1946. From then on, wheezing flared up frequently and severely during the months of September and October of each year, but remained mild and occasional the rest of the year. In 1950 her season had started earlier, in mid-July, and was still present on her initial visit in November. Skin tests to the usual variety of substances were negative, except for a 3+ scratch reaction to 1:200 Endo house dust extract and a 4+ intradermal reaction to the 1:1,000 dilution. Injections of house dust extract were begun, and by the end of November her asthma had disappeared. This could have been attributed to the end of her season. With continued treatment, however, she remained free of asthma the following July, August, September, and October of 1951. Treatment was stopped in March of 1952. She remained well until August of 1953, when asthma again set in, recurring every night with increasing severity, so that she resumed treatment on September 24. Symptoms disappeared after a few injections, the dosage being raised rapidly.

On May 7, 1954, she was subjected to inhalation testing, using hand nebulizers as set forth in Table II. Vital capacity was measured with a McKesson-Scott rubber bellows apparatus, three consecutive readings being taken on each occasion. Dilutions of all extracts were made with normal saline containing 0.5 per cent phenol.

The next morning she was tested with the following pollen extracts: *Amaranthus retroflexus, Chenopodium album, Salsola pestifier, Ambrosia elatior, Artemisia vulgaris, Cynodon dactylon, Agrostis palustris.* The extracts were of 1:100 concentration (diluted from a stock concentration of 1:20 in buffered saline containing 50 per cent glycerine). Each extract was administered twice, ten inhalations at a time, five to ten minutes apart. Other than slight coughing during or immediately after

the inhalations, no chest symptoms were induced and there was virtually no change in vital capacity measured five to ten minutes after each series of inhalations.

The experiments outlined above would appear to eliminate pollen and implicate house dust as the cause of the patient's seasonal asthma.

DISCUSSION

It is generally assumed that patients who are sensitive to house dust become worse in cold weather in consequence of their greater exposure to indoor dust at this time. How, then, can one account for a seasonal worsening of symptoms during the warmer months when time spent indoors becomes less? And why should the peak of symptoms during the summer months take place at different times for different patients?

It is as if the degree of exposure to house dust (speaking of the average day-to-day exposure) is really not the controlling factor in the situation. The recurrence of symptoms at the same time each year for each patient suggests that meteorological factors—particularly the temperature factor—somehow determine the seasonal exacerbations. It is known, of course, that sudden or marked changes in temperature, humidity, or barometric pressure may induce asthma or rhinitis in some individuals. However, if temperature is important here, its effect must be exerted in a way that is different from that associated with temperature change, since fluctuations in weather factors can hardly account for the prolonged periods of symptoms described herein.

It may possibly be that it is the sustained residence within a certain range of temperature that in itself serves to favor the onset or aggravation of symptoms. In certain individuals, exposure to a particular zone of temperature may set up a stress that becomes superimposed on the stress induced by the specific allergen, as a result of which the outbreak of symptoms may become facilitated, or symptoms already present may become exacerbated. If different individuals had different critical zones, so to speak, some set for high temperatures, others for low temperatures, within which such a flare-up or worsening of symptoms took place, the occurrence of house dust seasons for different patients at different times throughout the year could be explained.

On this hypothesis, increased exposure to house dust in cold weather may be less important in causing asthma in some individuals than the lowered temperatures to which they are subjected at this time.

Temperature may not always be the factor involved. Relative humidity might act as a precipitating factor in certain instances, and here too one must assume that each patient would react most readily when within the limits of his own particular critical zone. Other patients might require a certain combination of both temperature and humidity, or of other factors, to initiate or aggravate symptoms; and such combinations, as a result of the annual cycles of change in mean temperature, relative humidity, et cetera, could for a few individuals, depending on their particular suscepti-

bility, occur in both spring and fall, with a distinct subsidence of symptoms the rest of the year.

No matter what the explanation may actually be—and the answer is admittedly not clear for the time being—the fact nevertheless remains that in certain patients who are sensitive to house dust symptoms may become initiated or aggravated in warm weather instead of in cold weather. This circumstance creates difficulties in both the diagnosis and management of this distinctive clinical form of house dust allergy.

To begin with, the history is of no help in suggesting that house dust may be the offending agent when symptoms develop in warm weather, since other allergens are at this time also present in the air to complicate the picture. Added to this, if in the individual who becomes seasonally worse during the warm part of the year a positive skin reaction to house dust is the only one that is obtainable after complete testing, the physician will no doubt tend to question the significance of this reaction, or to ignore it, because of the current concept of what constitutes the house dust season. Indeed, if in addition to this definite reaction to house dust, the patient should also present some dubious or irritative reactions to pollen, the latter will inevitably be looked upon as being the real explanation for the seasonal symptoms. Special testing techniques (conjunctival, et cetera) may also yield equivocal reactions that may be seized upon as providing a more reasonable answer to the patient's problem. As the end result, the patient may be subjected to treatment for a supposed pollen or other inhalant sensitivity, when actually the sole sensitivity is to house dust.

The diagnosis of what may be termed "warm weather" house dust allergy may similarly be overlooked if, in reverse of the preceding situation, the patient shows pseudopodial skin reactions to one or more of the seasonal inhalant allergens in addition to house dust, or exhibits numerous dermographic reactions that are difficult to interpret. In such circumstances, the physician may again ignore a positive reaction to house dust, in view now of the definite reactions to other allergens that seemingly explain the picture. Nevertheless, it is possible at times for a dust reaction, in the presence of numerous other reactions, to be the only one that is actually of clinical significance, the others being merely of immunologic import on the one hand, or caused by nonspecific irritation on the other. Moreover, even if allergens such as pollen and fungi should be clinically important in any instance, the house dust factor may be equally important with respect to the seasonal symptoms.

In all of the preceding situations, treatment without house dust extract could be of only limited, if any, value. *Failure, therefore, of patients with seasonal symptomatology during warm weather to respond to specific therapy with factors other than house dust extract should always raise the question of a complicating overlooked house dust allergy.* To ignore a positive skin reaction to house dust because symptoms occur in warm weather

rather than in cold weather, and instead to give priority to positive or indeterminate reactions to other allergens obtained either by direct skin testing or by special testing techniques, may be misleading.

Finally, it should be evident that apart from difficulties in diagnosis, the physician in dealing with warm weather house dust allergy will frequently be faced with problems in dosage administration, inasmuch as the time during which a dust allergy may flare up may coincide with the season produced by another allergen.

The basic problem of separating a pollen season from a house dust season has recently been touched upon by Schiller and Lowell.[7] They report that in the course of experimentation with allergens by inhalation they were able to isolate a group of house dust cases whose symptoms were aggravated especially during the month of October. They point out that this dust season, coming as it does on the heels of the ragweed season in the New England area, necessarily causes confusion in the management of ragweed sensitive patients.

Their findings may not necessarily pertain to the New England area alone, or to one specific period of the year. If the seasonal patterns reported herein can be shown to take place in other parts of the country also, it becomes clear that there is no calendar portion of the year in any area that may not serve as a house dust season for some one patient. The predominant season for most patients may of course differ as to different areas as a result of local climatic factors.

SUMMARY AND CONCLUSIONS

It is generally believed that seasonal manifestations or exacerbations of respiratory symptoms in patients sensitive to house dust take place only during the winter or colder months of the year.

Evidence is presented to show that contrary to this belief one may at times encounter individuals who undergo seasonal symptoms during the warmer, instead of during the colder, months of the year. The exact time of occurrence of such a season, and its length, may vary in different patients, but for any one patient the season is as constant in time of annual recurrence and duration as a pollen season.

Since clinical house dust seasons are in effect distributed throughout the year, sensitivity to house dust must be kept in mind as a potential atopic factor in the production of seasonal asthma, rhinitis, or sinusitis, no matter what time of year symptoms occur.

The phenomenon of a seasonal occurrence of symptoms at different times of the year for different patients (in face of the fact that all are exposed to the same antigen to about the same degree at any one time of the year) is difficult to explain. The answer may lie in the catalytic effect on house dust allergy of meteorological factors, such as temperature and humidity. The hypothesis is advanced that (1) symptoms are provoked much more readily in some individuals when they become exposed to a

certain range or zone of values of one or more of these factors than when they are exposed to other values of the same factors, and (2) the zone within which symptoms become most readily exacerbated or precipitated is different for different individuals. Since this response to the effect of weather is brought about by more or less stable conditions persisting over a prolonged period of time, the mechanism involved must be different from that which comes into play when the weather fluctuates.

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MICHIGAN ALLERGY SOCIETY

Newly-elected officers of the Michigan Allergy Society are as follows:

President.....Sidney Friedlaender, M.D., Detroit

Vice President.....Kenneth Mathews, M.D., Ann Arbor

Secretary-Treasurer.....E. Oskar Schreiber, M.D., Flint

In addition to the officers, the following were elected to the Executive Committee: Alex S. Friedlaender, M.D., Detroit; Henry Beale, M.D., Toledo, Ohio; and Joseph Shaffer, M.D., Detroit.

THE OUTLOOK FOR THE TREATED ALLERGIC PATIENT

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FOLLOWING a talk on the subject of allergy before a neighboring county medical society, one of the physicians in the audience, during the period given to discussion, said to me, "This is all well and good, doctor, but please tell me the truth—how many cases of allergy have you ever really cured?" The present paper is an attempt to answer this pointed question. It appears to me that unless the clinical results obtained from adequate allergic management are exceptionally good, there can be but little justification for subjecting a patient to extensive diagnostic procedures and what often amounts to prolonged therapy.

It is not the purpose of this paper to discuss the procedures of allergic diagnosis and treatment. These should, of course, be carried out by a well-trained allergist. They include not only a good clinical history, physical examination, and the needed laboratory and x-ray studies, but a proper understanding of the interpretation, uses, and limitations of sensitization tests. In many instances, unfortunately, the performance of these tests is entrusted to laboratories and they are carried out by lay technicians whose understanding of the nature and clinical significance of such examinations is limited. Patients are referred for such studies in the hope that all that is necessary upon their completion is for the physician to give the patient an avoidance list on which are checked the items to which positive skin reactions are obtained. The patient is then expected to get well immediately by avoiding such substances. Hundreds of tests are often done, many of them to materials to which the patient is never exposed, since it is assumed that the longer the list the more comprehensive the study. Countless inhalants and foods are prohibited. The patient thus finds it impossible to follow these absurd directions. He experiences no immediate relief from these exacting and somewhat costly procedures and finally throws up his hands and gives up treatment altogether. Thus, another failure is chalked up against allergy—a conclusion which is obviously unwarranted, since neither diagnosis nor treatment were adequately and intelligently carried out.

Under proper circumstances and in competent hands, adequate allergic therapy includes correction and removal of associated pathology, such as undernutrition, anemia, and foci of infection; avoidance of any of the suspected causative agents; medication directed toward symptomatic relief; a period of hyposensitization with extracts of substances which are not

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easy to avoid; and, finally, psychotherapy if indicated. Of necessity, such a program is painstakingly long, often requiring time, patience and understanding on the part of both the patient and his physician. This is not entirely unexpected if one but realizes that allergic conditions have often been present for many years. Furthermore, and in all fairness, it is to be pointed out that the adequate treatment of allergy takes no longer than the adequate treatment of many medical conditions, i.e., diabetes mellitus, peptic ulcer, or heart disease.

I shall include here as allergic conditions, nasal allergy, both seasonal and perennial, bronchial asthma, skin allergy, including atopic dermatitis, urticaria and contact dermatitis, and a group of miscellaneous allergic conditions such as allergic headaches, gastrointestinal and joint allergy. I shall make no effort to present in support of my statements any specific statistical material, for such evidence is easily found in the literature and also because it is frequently and notoriously inconclusive. Rather, I shall draw upon clinical experience based on a review of many hundreds of instances of each of the above-named conditions seen both in the clinic and in private practice.

What then may the patient suffering with nasal allergy expect from allergic treatment? In the seasonal variety, commonly known as hay fever, he is very likely to experience gradually increasing freedom from the annoying nasal and ophthalmic manifestations. If these symptoms are also associated with asthma, the wheezing is definitely reduced. He need not in most instances live in fear of the approaching "season." He need not forever be in search of far-away pollen-free places to which to run. Because the allergist sees so many of these patients he knows just how to handle symptoms promptly and efficiently if and when they occur. In some instances, clinical results from pollen hyposensitization may be inadequate at first, but further investigation by skin tests may reveal the need for a change in the mixture of pollen extracts employed in treatment. Or, it may develop that the patient has been negligent in reporting regularly for his injections, or he has failed to carry out specific avoidance directions. Such changes in therapy frequently improve the clinical results. Following a pollen hyposensitization program for a period of four or five years, treatment may be discontinued without the recurrence of hay fever in many cases. What is even more important, proper attention not only gives the patient much needed relief but often prevents the development of seasonal asthma or of extension of pollen asthma late into the fall of the year. It most certainly avoids the occurrence of any nasal complications such as sinusitis and mucous polyps.

If this is true of seasonal hay fever, it is also true of perennial nasal allergy. In uncomplicated cases of allergic nasal allergy, the therapeutic results are excellent. Nasal obstruction, embarrassing sneezing, and rhinorrhea, the loss of smell and usual dry throat caused by mouth breathing are remedied. Nasal polyps are prevented, and nasal infection is avoided.

In children, early treatment of nasal allergy also prevents the development of bony deformities in the hard palate (gothic arch), as well as dental deformities. Naturally, such improvement does not result from allergic treatment alone, if the patient has already developed nasal infection. Obviously in many of these instances it will be necessary to secure for the patient rhinologic care in order to correct anatomic abnormalities, provide proper nasal drainage, and help erradicate infection.

How often has an allergist been told by the grateful mother of the treated asthmatic child that for the first time since the child has had asthma, treatment has not only relieved the severity and frequency of the attacks, but the child has hardly missed any time from school. He has put on weight, and is less irritable and fretful. There is no doubt that early etiologic diagnosis and treatment of an allergic cough or bronchial asthma in an infant or child does away with disturbing frequent wheezing and sleepless nights. The child's emotional reaction to his environment is changed. There are fewer attacks of bronchitis with fever and asthma. If no pulmonary complications are present, the therapeutic results are no less gratifying in the adult. However, is it fair to charge against allergy the failure to obtain improvement in a patient whose allergic bronchial asthma has been neglected for many years? When this patient in desperation finally seeks help, he often already shows evidence of pulmonary fibrosis and emphysema, both of which are responsible for his increasing dyspnea and cough; or, as a result of a continuous, untreated, mismanaged wheezing and cough, he may have developed chronic bronchitis or even bronchiectasis. How reasonable is it to expect treatment directed towards correction of allergic factors to affect these irreversible structural pulmonary changes—changes which could most certainly have been avoided or minimized if only allergic therapy had been instituted early? Fortunately, the medical profession is becoming more and more aware of the need of early attention to allergic conditions. Mothers are no longer told to forget about the child's asthma, or that the child will "outgrow his asthma." Allergic asthmatic children are no longer dismissed with a shrug of the shoulders and told that "there is not much that can be done about their condition." An enlightened medical profession realizes that a great deal can be, and is being, done for these patients—that even those with long-standing asthma can be rehabilitated to various degrees by careful medical and allergic care. Furthermore, the internist trained in allergy occasionally discovers that the patient whose symptoms simulate those of asthma may actually have heart disease, cardiopulmonic failure, or may have tuberculosis or some form of pulmonary malignancy—pathology which thus discovered sufficiently early yields to proper treatment.

The patient suffering with skin allergy is in some respects more fortunate, due to the fact that the layman has developed a high index of suspicion that his "eczema" or his "hives" may be allergic. If ordinary treatment does not help him, he soon wants to know whether his condition

is allergic and, if so, what is it that is causing it. An allergic study in such instances is often very rewarding. In the case of contact dermatitis, the survey need not be extensive; a few patch tests will tell the tale. The results are frequently dramatic. The severe dermatitis of the scalp and face disappears after the shampoo, hair dye, mascara, nail polish, or other cosmetics are discontinued. The eczema of the hands clears up when the nature of the contactant is recognized and soap is eliminated. Removal of occupational contactants, avoidance of plants and weeds, the administration of steroids, and, in the case of poison ivy dermatitis, hyposensitization are frequently quite effective. When urticaria is part of a serum disease type of reaction from drugs or antibiotics, recognition of the cause and its removal, as well as administration of antihistaminics and steroids, give the patient quick relief. His anxiety is also reduced because it is possible under these circumstances to give the patient a good prognosis. Chronic recurrent intractable urticaria, when allergic in origin, is often well controlled and improved.

There has been some controversy about the nature and the value of the type of skin tests employed in the etiologic diagnosis of atopic dermatitis, a condition characterized by the appearance of skin lesions usually beginning in infancy and having a typical distribution. The allergy is familial. If not treated, it may spread later in life to the rest of the body and give rise to secondary infection of the skin, lichenification and hyperkeratosis. Some dermatologists question the allergic nature of this condition and believe it entirely of psychosomatic origin, a view which is not warranted by all the available evidence. In the first place, the very word, "atopic," indicates an allergic factor. Secondly, a patient affected with severe and persistent pruritus becomes sleepless, irritable, and emotionally disturbed. He is distressed by his appearance. It is often difficult to tell the relation between cause and effect. As a rule, however, the patient with an atopic dermatitis, who is carefully studied from a medical and allergic viewpoint, stands a much better chance of obtaining relief than the patient whose skin is traumatized by all sorts of local applications and x-ray and then told that his condition is due to "nerves." I submit that it makes little sense to label a condition as allergic and then deprive the patient of allergic studies and allergic treatment.

Advances in clinical allergy have helped to focus our attention on the frequent reactions which develop from drugs, foreign sera, antibiotics, biologic products, and local applications. The early recognition of the allergic nature of these conditions, and the avoidance of the causative agent, saves many a patient an increasingly severe dermatitis or urticaria and many other untoward and sometimes serious complications.

In instances of various types of allergic involvement, where emotional factors are of importance, psychotherapy is included as part of management. The allergic phase of the treatment under these circumstances may thus increase in importance because of its added psychotherapeutic effect.

The patient feels that at last someone has become interested in him and is willing to guide him out of his difficulty.

The patient suffering with nasal, bronchial, or skin allergy has, generally speaking, an excellent chance of either complete recovery or of keeping his condition well under control, provided the diagnosis is accurate and treatment is started early. Certainly, this patient, suffering as he does with a reversible lesion, has an infinitely better chance of relief than do patients suffering with chronic recurrent diseases. One can truthfully answer the question, "How many cases of allergy did you cure?" by stating that many allergic patients get well, well enough to be happy and comfortable and relatively symptom free. However, the allergist cannot do this job unaided. Once the diagnosis is made and treatment is instituted, it becomes necessary to get the co-operation of the family physician. After all, it is he who must, in many instances, carry out the treatment advised by the allergy consultant. Such treatment can be intelligently applied by him if the physician understands the principles which are involved and if he is convinced that the therapeutic results are worth the effort.

Notwithstanding costly and time-consuming temporizing and wishful thinking, only a few patients "outgrow" their allergies; another few lose their symptoms because a coincidental change in environment sometimes removes the causative factors. For the remaining large group of patients, failure to provide adequate allergic treatment frequently has disastrous effects. The patient continues to suffer with the recurrent allergic condition, he loses time from school or from work, life becomes a seemingly endless struggle with annoying and incapacitating symptoms, and, inevitably, secondary complications develop which make treatment difficult if not impossible. After all, the purpose of medical care is to reduce mortality and morbidity. It is to render life more pleasant and more comfortable. Allergic therapy early and properly instituted will, to paraphrase George Piersol's expression, "not only add years to life—but add life to years."

Bigelow Apt.

ALLERGY SESSION OF THE AMA, CHICAGO, 1956

Any member who wishes to present a paper at the Allergy Session of the American Medical Association convention to be held in Chicago, June 11-15, 1956, should write to the secretary, Lester L. Bartlett, M.D., 550 Grant Street, Pittsburgh 19, Pennsylvania, for "Suggestion for Authors of Section Papers" and "Rules of the Section." Abstracts will be accepted for possible inclusion in the program until January 31, 1956.

NASAL SURGERY IN ALLERGY

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OBSTRUCTION and sinus infection, when associated with allergy, are the chief indications for nonallergic therapy. Surgery is indicated whenever there are irreversible changes in the tissues and when infections persist following antibacterial therapy and/or drainage procedures.

For convenience we classify nasal obstruction as acute, intermittent, and chronic. Assuming we are dealing with an allergic nose, we can classify our cases into acute and chronic, with and without infections. The acute allergic nose should not be traumatized by surgery or local medication. When an acute infection is present and resists systemic treatment, drainage procedures may be indicated. The intermittent nasal obstruction of allergic origin should be controlled by management of the allergy.

Recent works have emphasized the importance of observing the upper and lower lateral cartilages and their action on inspiration and expiration when the patient is both in the upright and reclining positions. The mobile part of the nose plays a much more important role in respiration and in the sensation of obstruction in the nose than is generally recognized. This may explain why a patient with a deviated septum that appears to be blocking one side of the nose complains of obstruction on the other side. For this reason, in all allergic individuals with a deviated septum, one should consider the possibility of abnormality in the mobile part of the nose as well as the allergic factor which is causing the obstruction. Correction of a deviated septum producing symptoms is indicated, but we must eliminate general conditions, such as hypothyroidism, hypotension, allergy, or local conditions, such as abnormalities in the mobile part of the nose, such as a thickened columella, disturbances in the structure of the nasal valves, and other structural defects. If the septum is producing the obstruction in the nose, we can expect results from a submucous resection. The removal of all the cartilaginous and bony portion of the septum, except a small portion left for support of the tip of the nose, as is sometimes done, allows the septum too much mobility. We should retain as much support as possible by leaving the cartilage and bone where logical, or, if necessary, taking it out and replacing it in the midline.

There can be changes in the septal mucosa from allergy, but most of these changes occur on the lateral wall and roof of the nose. The changes in the inferior turbinates are likely to be reversible when due to allergy. If an inferior turbinate is producing obstruction of the nose, it can be

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fractured toward the lateral wall, injected with sclerosing solution, or a submucous resection of the turbinate bone performed. The surface epithelium of the nose should never be destroyed by any method. Rose polyps occurring on the posterior end of the inferior turbinate should be removed. The edema in the posterior portion of the inferior turbinate which occasionally occurs from allergy will subside with proper antiallergic management.

Nasal polyps of allergic origin first appear on the roof of the nose. Small polyps usually recede under proper management of the allergy, and they should be given an opportunity to do so. Some of the olfactory end-organs are in this area and may be damaged as the polyposis increases. If there is any indication for the use of the cortone preparation in the nose, it is in this type of case, but I have been disappointed in the results obtained from its use.

As these polyps increase in size they become more discrete, pedunculated, and the tissue changes are less likely to be reversible. The smaller the pedicle in relation to the size of the polyp, the less chance it has of reversibility. If the polyps do not subside under management of the allergy, they should be removed, and should also be removed when proven to be irreversible.

Polyps should be removed by placing the wire of a nasal snare over the polyp as near the base of the pedicle as possible, partially closing the wire and pulling the polyp from its attachment. The more polyps there are in the nose, the more difficult it is to see their attachments; and the longer they remain, the more damage there is to the nasal mucosa, the greater the possibility that the sense of smell will be destroyed, and the less chance the nose has to function properly. When secretion and epithelial debris are retained between the polyps, a foreign body reaction develops. As the polyposis increases, the polyps become attached lower and lower on the nasal walls, and secondary infection is always present in these neglected cases.

Polyps from the floor of the ethmoid sinuses, that is, between the middle turbinate and the lateral wall of the nose, are usually caused by infection in the ethmoid cells. When one sees this and especially when there are no polyps on the roof of the nose, suspicion not only of allergy but of superimposed infection should be aroused. One seldom sees patients when the polyps first develop, but may see the patient after there are polyps on the roof of the nose and in the middle meatus. Under antiallergic management the polyps may disappear from the roof of the nose, and in the middle meatus. Under antiallergic management the polyps may disappear from the roof of the nose, but remain in the middle meatus. The middle meatus would also return to normal if the ethmoids were not, or have not been, infected. The anterior end of the middle turbinate may be edematous, either from an infected cell in the middle turbinate or an allergic change in the mucosa.

Solitary polyps seen in the nasopharynx may originate from an antral hyperplastic sinusitis, being produced by a prolapse of the antral mucosa. These polyps will recur unless the infection is controlled by removing the lining mucosa of the antrum.

CASE REPORT

B. S. R., aged nine, was examined in August, 1947. He complained of nasal stoppage, colds during both winter and summer, with sneezing during the winter. He was tested for allergy in 1946, and was treated with house dust extract. His tonsils and adenoids had been removed at age five, presumably because of nasal obstruction. Polyps were observed in the nasopharynx one year later, and a polypectomy was performed in March and again in June, 1947. There was a family history of allergy, in that the mother had hay fever.

On examination a large polyp was observed in the nasopharynx arising from the middle meatus on the right side, with a moderate amount of mucopus. The nasal smear showed an occasional eosinophil, many leukocytes and bacteria. The patient reacted positively to house dust, and x-ray examination showed a generalized density in the right antrum.

The parents were told that it would be necessary to remove the source of the polyp, which was the antral mucosa. They were afraid of injury to the teeth from a Caldwell-Luc antral operation, but agreed to the removal of the polyp and an antral window. Two months later the patient was seen because of a cold. The antrum was washed, and no pus was seen. Three months later a prolapse of the antral mucosa in the inferior meatuses was noted, and five months later a polyp was seen in the middle meatus, and the inferior turbinate was enlarged. X-ray showed a generalized density of the right antrum. One year later a polyp extending into the nose from the antrum was seen. A Caldwell-Luc operation was performed one year from the date of original diagnosis, and it was found that the antral mucosa had filled the antral cavity and protruded into the nose through the inferior and middle meatuses. The patient made an uneventful recovery and has no evidence of injury to the teeth. Time has proven the positive reaction to dust, but there has been no indication that the nasal polyp was due to allergy.

ALLERGY WITH SUPERIMPOSED SINUS INFECTION

Pathogenic bacteria are always present in the front part of the nose trying to break through nature's defense, and although a patient presents himself with an allergy today he may next week suffer a superimposed infection.

In these patients the importance of repeated study of the nasal secretions and x-ray findings of the sinuses cannot be overemphasized. We are prone to be satisfied with one nasal smear or one x-ray study of the sinuses. X-ray films can be used to follow the progress of either or both the infection or the allergy in the sinuses. There is a great deal of knowledge to be gained from both negative and positive x-ray studies when these are correlated with clinical findings and history.

Hyperplastic sinusitis is very easily confused with allergic sinusitis. In either disorder there may be polyps, uniform thickening of the sinus mucosa, and no purulent discharge. One should be suspicious of a hyper-

plastic sinusitis when roentgenograms show uniform involvement of some but not all of the sinuses.

Purulent sinusitis should not be confused with allergic sinusitis because the history, nasal, laboratory and x-ray findings are different. Polyps do not occur as frequently in purulent sinusitis except in the ethmoid sinuses. When infectious and allergic responses are seen in the nasal accessory sinuses, each should be managed as though the other were not present. Elimination of infection should include systemic treatment with antimicrobial agents when necessary, local treatment, drainage procedures and removal of the infected mucous membrane of the sinus. If one is not certain which treatment will accomplish results, the most conservative method should be used. Through experience one can often determine from the history and the clinical and x-ray findings which type of treatment is required.*

In chronic sinus infection, systemic treatment with antimicrobial drugs should be used for at least two weeks, and vitamin B-complex should always be prescribed with the antimicrobial agents. Medications including antimicrobial agents can be instilled into the maxillary sinuses through the natural ostia or inferior meatuses or into the other sinuses by displacement. Nasal sprays containing the antimicrobial agents are of questionable value and are more likely to sensitize the patient to the antimicrobial used.

The frontal and ethmoid sinuses have dependent drainage, and we are seldom required to assist nature in draining them. The maxillary sinus does not do as well because the ostium is not placed dependently. In the antra the cilia must function to maintain proper drainage. Drainage can be established temporarily by irrigation of the antra. Should the antra fail to respond to irrigation over a reasonable length of time, permanent and dependent drainage can be established through a naso-antral window in the inferior meatus.

If one decides after examining the patient that these methods might fail or when the previous mentioned methods of treatment do fail, then the patient and the doctor should decide between palliative treatment or an attempt to eliminate the superimposed infection. If palliative treatment is chosen, one should realize that extension of the infection or complications may occur. If an attempt is to be made to eliminate the infection, the above-mentioned procedures should be combined with the removal of all the irreversibly diseased tissue, as would be done by surgery on diseased tissue in any other part of the body.

MAXILLARY SINUS SURGERY

To accomplish the complete removal of diseased tissue from the antrum, an approach is made through the canine fossa. All lining mucosa can and must be removed, the bony inferior meatal wall is taken down, and the

membranous wall is detached from above and used as a flap on the floor of the antrum. This acts as an epithelial graft eventually covering over the tissue that fills in the antral cavity. The ideal end-result is a small cavity with dependent drainage connected with the nose and covered with nasal epithelium.

ETHMOID SINUS SURGERY

The ethmoid sinuses are approached surgically by the transantral, intranasal or external routes.

Transantral.—When both the antra and ethmoid sinuses are involved, the transantral combined with the intranasal route offers an excellent approach. It is, however, a physical impossibility to exenterate the supra-orbital ethmoids in any but an external approach.

Intranasal.—Exenteration of the ethmoidal cells intranasally is sometimes a difficult procedure because of the limited working space. Since all cells should be exenterated, one should choose the method of approach best suited to the individual patient and the surgeon.

External.—The external approach to the ethmoid sinus is popular because one can be more certain of a complete exenteration of all cells, and because this approach is relatively safe for the surgeon who only does an occasional ethmoid exenteration.

It is important to protect the middle turbinate in all ethmoidal procedures, as it is an important physiologic structure and it should not be removed except on rare occasions. The ethmoid space where the cells were removed heals by a migration of nasal epithelium over the cavity formed, with the exception of the space left by the exenteration of the supra-orbital ethmoid cells, which is filled in with orbital contents.

The sphenoid sinus for all practical purposes can be considered as a posterior ethmoid sinus.

FRONTAL SINUSES

The frontal sinuses seem to have more recuperative power than the other sinuses, probably due to dependent drainage. Although the frontal sinus is diseased, the elimination of the infection from the antra and ethmoid sinus may clear it up. Should the frontal sinuses not clear, there will be clinical evidence of disease around the frontal ostium. If persistent, the diseased lining of the frontal sinus must be removed, and the approach is from an external incision. Any supra-orbital ethmoid cells present should be exenterated and all lining removed. The floor of the frontal sinus is removed to give access to the cavity for the removal of the entire lining mucosa. The secret of success is the removal of every

vestige of the frontal mucosa and removal of any infected ethmoid cells or correction of any high anterior deviation of the septum. If this is done, there is no reason to skin graft the naso-frontal duct or insert a tube of any type to keep the frontal sinus open. The frontal sinus will fill in as the antral cavity does and is sometimes completely obliterated.

Instillation of tubes without removal of the lining mucosa of the frontal is only a drainage procedure and is comparable with an antral window. The indications for such drainage procedures are entirely different from those requiring the removal of the actively infected lining mucosa, but drainage is not a substitute for removal of the diseased tissue.

As suggested by Lynch, the external frontal operation can be performed without producing a deformity by making the incision under the brow and along the side of the nose. The indications for external frontal procedures are not always clear, because one cannot tell how much the diseased ethmoid sinus is blocking the frontal sinus, nor can one always interpret correctly the x-ray films of the frontal sinuses because the sinuses vary in size and depth. The interpretation is sometimes based on a comparison of the two frontal sinuses, and when the same density in the x-ray films exists in both the interpretation of the density is difficult.

CASE REPORT

J. M., a white man, aged forty-six, had his symptoms begin with a severe cold three and one-half years ago. Treatment for sinus infection was undertaken by medication and antral irrigation for six months, without benefit, so an antral window was made on each side. Asthma developed on penicillin administration. There was no family history of allergy. The patient was referred to an allergist by another otolaryngologist, who tested and treated him with injections of pollen and house dust extract, which did not relieve the asthma. After four months he was told that the asthma could not be relieved until his nose was "cleaned up."

It was the opinion of the referring allergist that the asthma started from an allergy, because of a blood eosinophilia of 18 per cent. An infection was known to be present but thought to be secondary. The patient had received antimicrobial agents, cortisone, and other medication, but nothing seemed to help him. Present treatment consisted of four minims of adrenalin three to eight times daily, aminophylline, cortisone, ACTH once each week, Tedral®, and hyposensitization. The infection in the nose was believed to be the "trigger mechanism" for his asthma, and the allergist thought more complete surgery was necessary.

The referring otolaryngologist explained that the patient had been treated for infection with antimicrobial agents and drainage procedures, but had not responded.

A depressed nasal bridge, negroid type nostrils, ballooning of the upper lateral cartilages, and normal mucous membrane were noted on examination. There was a thick purulent discharge in the nose and a thick pus and mucus in the middle meatus that stretched like rubber. The nasal smear contained many bacteria and an occasional eosinophil. The middle meatus was filled with polyps, epithelial debris, and a brown elastic substance packed in between the polyps. Those present were limited to the middle meatus, indicating infection as the cause of the polyposis. The middle turbinate was pushed toward the septum, which was deviated high and

to the right, the right antrum was filled with thickened mucosa, and the opening in the inferior meatus was closed.

X-ray examination revealed a generalized density of the ethmoids and maxillary sinuses bilaterally, and the left frontal sinus was slighty larger than the right and uniform in density.

A transantral ethmo-spheno-frontal operation was performed on the left side under local anesthetic, and the right antral window was enlarged. The antral mucosa was removed, and transantral exenteration of the posterior ethmoid cells was done, as well as intranasal removal of the anterior cells. The anterior wall of sphenoid was taken down, the polyps were removed, and the middle turbinate was fractured toward the septum. The antral mucosa was found to be thick, tough, polypoid, and cystic. Present also was gelatinous material that was difficult to remove with a suction because of its tenacity. Some of the cellular partitions in the ethmoid had been destroyed. The mucous membrane and contents removed from the ethmoid cell were essentially the same as that removed from the antrum. On the third day the patient developed a severe attack of asthma, and medication had to be increased. In two weeks he was discharged from the hospital improved.

Four months later a transantral ethmo-spheno-frontal operation was performed on the right side. The high deviation of the septum would have been corrected but for the possibility of producing a status asthmaticus from extensive surgery. The septum was not blocking the nose, nor did it prevent access to the anterior ethmoid cells. The left frontal had remained clear following antral and ethmoid surgery, therefore it was decided not to correct the septum. After the surgery was completed the ethmoidal area was inspected again for any cell that could have been overlooked, and none were found.

Infection was not as active on the right side, probably because of improved drainage from enlargement of the antral window. The pathologic findings were essentially the same as on the opposite side. The patient showed immediate improvement, followed by an exacerbation of his asthma on the fifth day. He improved rapidly and was discharged from the hospital on the tenth day. He continued his hyposensitization and was observed frequently.

Six months later the left side of his nose appeared to be normal, although pus and polypoid changes were seen in the right middle meatus anteriorly. All x-ray films of the patient's frontal sinuses were reviewed and new films were taken. At no time was the right frontal sinus more dense than the left. In two of the pictures made in 1952 there seemed to be an area of density in the left frontal sinus near the upper outer portion, but otherwise the x-rays of the frontals showed them to be uniformly dense.

External frontal (Lynch type of incision) and partial submucous resection of the nasal septum was performed twelve months later. The floor of the frontal sinus, all supra-orbital ethmoid cells, and all frontal mucosa were removed. All intranasal ethmoid cells were found to have been exenterated. The bone causing the septal deviation was removed, and the septal mucosa was found to be thicker than normal over this area. Either the right frontal was more diseased than the left, which was not evidenced on x-ray films, or the compensatory hypertrophy of the septal mucosa opposite the upper lateral cartilage, or the high deviation of the septum prevented the right frontal sinus from eliminating the infection. From these observations one would conclude a high anterior septal deviation should be corrected in patients requiring frontal sinus surgery.

Since the last operative procedure the patient has not suffered from asthma except after long automobile trips and when exposed to glue. All medication has been discontinued, and proper management of the patient's allergy should prevent a return of the asthma.

SUMMARY

Many physicians and especially those practicing allergy are under the impression that sinus surgery does not accomplish the desired results, and every allergist has seen patients who have had sinus surgery with poor results. The allergist probably will see more of these patients than any other physician, because if the patient had obtained good results from surgery he would not be seeking help from an allergist. Most of these patients not benefited by surgery are probably allergic individuals who did not require surgery or who required both surgery and allergy management. Some otolaryngologists realize the grave mistake of not recognizing allergy and of attempting to cure all sinus disease and disorder by surgery.

For years we have taught, and we are now teaching, conservatism. There is a possibility, however, that we have overdone it. We have created such a fear of sinus surgery in some of our younger men that they do not recognize its indications. With some allergists opposed to sinus surgery and with some otolaryngologists hesitant in recommending surgery on the allergic individual, the allergic patient with irreversible nasal and sinus pathology is likely to be deprived of the advantages offered by surgery.

1089 Madison Avenue

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FOOD SENSITIZATION AS A CAUSE OF PERENNIAL NASAL ALLERGY

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IN 1950 in a historical review of allergy in otolaryngology Hansel[1] pointed out that, although the allergic nature of vasomotor rhinitis was first suggested about 1906, nasal allergy as a definite clinical entity was not established until about fifteen years later. Within the next five years allergy as the cause of chronic paranasal sinus disease began to gain recognition. However, the management of chronic nasal and sinus disease was dominated by surgical thinking at the time, and there was neither the feeling nor the inclination in otolaryngology to become oriented in antigen-antibody reactions. This indifference to allergy, in a specialty preoccupied with the problem of infections, lasted, in spite of the pioneering efforts of Hansel, until a little more than fifteen years ago.

The advent of the sulfonamides and, more recently, the antibiotics has greatly reduced the time and energy devoted to the management of infection, and at the same time has shown that certain acute and chronic conditions in the ear, nose and throat, previously considered to be primarily infections, did not respond to these drugs which ordinarily control and cure infection. Thus, another etiology had to be sought for many of these conditions, and allergic investigation and management have provided the answer in many instances.

In my opinion, nasal allergy is responsible for most of the complaints in the practice of rhinology and also accounts for a considerable segment in the practice of the general allergist. Allergic rhinitis includes not only typical seasonal hay fever, but also the conditions known as vasomotor rhinitis, hyperaesthetic rhinitis, intumescent rhinitis, catarrhal rhinitis and hypertrophic rhinitis. All of these conditions are merely varying degrees of, or synonyms for, perennial nasal allergy, often with superimposed secondary infection. Some cases of atrophic rhinitis, too, are the end result of perennial allergic rhinitis of many years' duration.

The oft-described pathology of allergic rhinitis may be termed allergic inflammation of respiratory mucosa with the characteristic findings of this condition, in contrast to inflammation due to acute or chronic infection. Of fundamental importance is the fact that an allergic reaction of the respiratory mucosa tends to involve all of the mucosa simultaneously, though not necessarily to an equal degree. A clinical sinusitis complicating an allergic rhinitis is thus understandable, since the sinuses are diverticula of the nasal cavity lined by an extension of nasal respiratory mucosa. The

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characteristic allergic edema and hypersecretion in the sinus are part of the nasal mucosal reaction, and produce no special symptoms while the sinus ostium remains unobstructed. However, occlusion of the ostium results in retained secretions, and the symptoms of a clinical sinusitis arise. In our experience, over 90 per cent of chronic sinusitis is based upon an allergic rhino-sinusitis with obstructing edema of the sinus ostia. The resultant stasis predisposes to infection, and infection superimposed upon a chronic allergic state tends in turn to become chronic.

CLINICAL DIAGNOSIS OF PERENNIAL ALLERGIC RHINITIS

The symptom history, the appearance of the nasal mucosa, and the cytologic examination of the nasal secretions give presumptive evidence of an allergic cause for a chronic rhinitis, but the final proof remains in the response to the therapeutic test. The nasal symptoms are variable depending upon the duration, the amount of secondary infection, and upon the allergens involved, inhalants tending to produce paroxysmal sneezing, intermittent nasal blocking and watery discharge, and foods tending to produce a more continuous obstruction and a copious mucoid discharge. The less dramatic but more frequently encountered complaints of chronic nasal stuffiness and postnasal discharge are just as typical of an allergic rhinitis, in our opinion, as are the sneezing, watery nasal discharge, severe nasal obstruction and lacrimation of hay fever.

The nasal examination may reveal a typically pale, edematous and boggy membrane bathed in a clear or cloudy tenacious mucus, but in some cases of chronic nasal allergy the nasal mucosa may be reddened, congested and with the septum and middle turbinates bilaterally covered with dry crusted secretions. Nodular hypertrophy of the posterior turbinate tips is a frequent finding in perennial nasal allergy, and less frequently the chronic edema may result in the formation of polyps, especially on the middle turbinate and projecting from the ethmoid cells.

Cytologic study of the stained nasal smear in allergic rhinitis will show the presence of eosinophils in varying amounts, depending upon such factors as the concentration of the nasal secretion and the degree of superimposed secondary infection.

In the final analysis, proof that a nasal allergy is the reason for chronic nasal symptoms depends upon establishing the specific causal diagnosis by the therapeutic test: if removal of a specific substance or treatment with an extract of this substance relieves the symptoms, and if the symptoms recur on re-exposure, or after the treatment has been discontinued, it may be assumed that the particular substance is responsible for the symptoms.

The yearly recurrence of seasonal pollinosis makes both the clinical and the causal diagnosis of a seasonal allergic rhinitis relatively easy for the allergist, and the patient readily accepts the complete diagnosis. On the other hand a patient, as well as his referring physician, may be hesitant

about accepting a clinical diagnosis of perennial nasal allergy without the conclusive proof by therapeutic test of the causal diagnosis.

CAUSAL DIAGNOSIS OF FOOD SENSITIZATION IN PERENNIAL NASAL ALLERGY

There is universal agreement among general allergists and otolaryngologists practicing allergy concerning the primary importance of house dust as an inhalant allergen causing perennial nasal allergy. No such close agreement seems to exist as to the relative importance of food sensitization as a causative agent. Whereas a dust allergy is established through a standard procedure employing inhalant skin tests followed by a therapeutic trial of dust hyposensitization, there is no such generally accepted diagnostic technique for the detection of food allergy.

What are the diagnostic techniques one may employ in the analysis of patients with nasal symptoms presumably due to foods? What history of nasal symptoms raises a suspicion of possible important allergic food factors? Earlier I stated that food sensitization tended to produce a more continuous type of nasal obstruction with copious mucoid discharge than was caused by inhalants. Even in an uncomplicated food allergy, this is not necessarily so. Sometimes foods can be responsible for intermittent nasal symptoms with acute attacks of sneezing, watery drainage, stuffiness, and even malaise and fever, all of which may last for several hours to several days with relative freedom from symptoms between frequent attacks. Another type is characterized by constant mild nasal stuffiness with a daily increase in symptoms of increased blocking and secretion occurring in the late afternoons and upon arising in the morning. It must be remembered that many cases of perennial nasal allergy are due to both food and inhalant sensitivity, and these dual factors can complicate symptomatology beyond the recognition of any pattern. Any case of chronic allergic rhinitis which, after considerable manipulation of dust hyposensitization, gets consistent partial relief, should be suspected of a concomitant food sensitivity.

Certain clues in the history have been particularly helpful in identifying those cases in which a food workup must be anticipated. A relatively constant pattern of nasal symptoms not influenced by season or environment suggests an uncomplicated food sensitivity. Other than nasal symptoms, undue fatigue or drowsiness after meals, migrainous or vascular-type headaches, and frequent gastrointestinal symptoms of diarrhea, so-called "spastic or nervous colitis," gallbladder complaints, bloating, and flatulence can all be frequent additional indications of food allergy. Food dislikes and suspicions of the patients should never be ignored. This may be more reliable as an indication of the existence of a food sensitivity, but may be misleading as to specific diagnosis.

Several diagnostic techniques for specific food allergen diagnosis may be used. Skin testing, food diary and symptom records, elimination or trial diets followed by food additions, and finally individual food testing

are the principal methods for food study. I have listed these in the above order because it was in this particular order that these techniques were incorporated into our own otolaryngologic allergy practice. It should probably go without saying that the latter two would never have been attempted if the first two had given satisfactory results in our allergic workups. However, the selection of a diagnostic technique will be determined not only by the efficiency of the method, but by the convenience and availability of the patient, by economic factors, and, unfortunately, by the time the physician can devote to individual patient's allergic workups.

The value of skin testing in food diagnosis has proved to be practically negligible in my own experience. Regardless of one's opinion concerning the value of such skin testing, it is very easy to find recognized authorities whose writings will support or disagree with any opinion pro or con. Rowe[2] and Rinkel[3] in their monographs on food allergy emphasize the fallibility of skin tests and the uselessness of doing the tests without supplementing them by other diagnostic methods. Samter[4] in a recent report quotes a clinical experience with two groups of fifty patients ill with various allergic diseases; in one group etiologic diagnosis was attempted exclusively on the basis of skin testing, and in the other group the patient interview and history without skin tests was the basis of the diagnosis. Samter's findings were "an approximate diagnosis was made in less than 10 per cent of the patients of the first group" and "an adequate diagnosis (resulted) in almost 70 per cent of the patients of the second group." He also emphasized that "the fallacy of the positive skin test is responsible for a considerably larger number of incorrect diagnoses in allergy than the fallacy of the negative skin test." This would be a probable argument in favor of scratch testing for foods rather than intradermal testing.

The use of a food diary and symptom record has been very inefficient in helping me to establish a specific causative diagnosis of a frequently ingested food, but it may clearly indicate causal relationship between infrequently eaten foods and exacerbations in nasal symptoms. In the latter case, the patient will often give the same information in a well-taken history. The food diary and symptom record does provide a quantitative food intake history and will reveal those foods which are eaten frequently enough to require individual food testing and also prevent conflicts with our basic diet.

Our attempts to demonstrate "a cause and effect relationship between the ingestion of a given food and the production or accentuation of specific (nasal) symptoms"[3] seem to be best served by the use of the individual feeding tests of Rinkel et al[3], or the combination of the basic elimination diet and the individual food testing techniques. These tests, too, have certain limitations, being very dependent upon the patient's intelligence and co-operation in following precise dietary instructions and restrictions, and the tests are certainly subject to human error by both

patient and doctor. In a patient with both food and inhalant sensitivities responsible for the nasal allergy, the food search is best carried out after adequate hyposensitization of the inhalant allergy has been effected.

BASIC DIET

Evening before starting diet take one tablespoonful of Epsom Salts in water, *or* two tablespoonfuls of Milk of Magnesia.

Take no other medication while on diet. Put nothing in the mouth except water and the foods listed below. This includes candy, chewing gum, etc.

EAT *ONLY* THE FOLLOWING FOODS:

Meat:	Well cooked lamb or fresh fish (not canned)
Fruits:	Banana Prunes Fresh or stewed pears (not canned)
Cereal:	Oatmeal Rice
Fresh-Vegetables: (not canned or frozen)	Spinach Turnips Carrots Endive Squash Sweet Potato Rice Celery
Beverage:	Water Tea (sugar if desired, but no cream or lemon)
Preparation:	May use salt, pure olive oil, pure maple sugar and cane sugar

DO NOT eat Ry-Krisp, crackers or breads!!

The basic elimination diet (see chart) is one we have arrived at through the influence of several authors, and in it we attempt to eliminate all of the more common foods whose order of probable incidence of sensitivity is known. This basic diet is followed carefully for four days by the patient in order to "unmask" his possible "masked" food sensitivities. Then on the fifth day, at noon feeding, the first of the individual food tests, according to the Rinkel technique, might be given. If no symptoms are produced by this feeding, on the following day at noon a second food test is given. This may be continued for a total of seven foods and no more, since it is felt that foods which have been out of the diet twelve days or more will require more than one feeding to produce possible symptoms. If any of the feedings produce acute nasal allergic symptoms, there must be a forty-eight hour wait for the acute phase to subside before adding a new feeding test. This diagnostic method is used when circumstances dictate as rapid a food evaluation as possible.

The separate individual food tests can be performed one at a time. Thus, one food is eliminated for four days and a noon feeding of the food prepared according to directions taken, and the postprandial symptoms

recorded for one hour after the first feeding and for thirty minutes after the second feeding, for comparison with thirty minutes of preprandial symptoms. The symptoms are checked on the sheet shown in Figure 1.

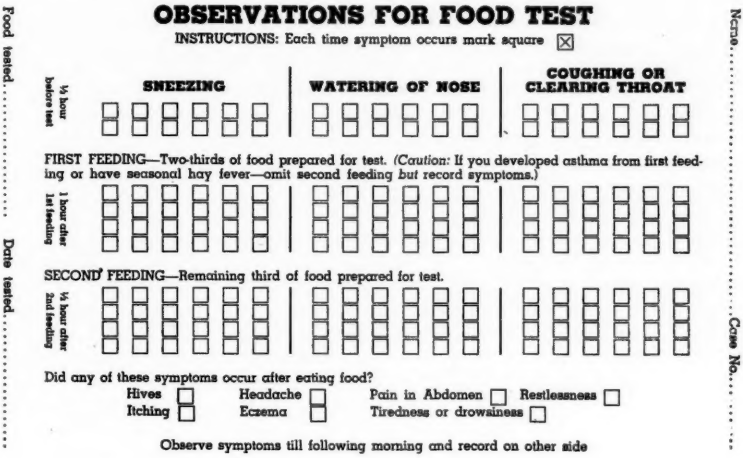

Fig. 1.

The foods which occur several times daily, once daily, or once every other day in the patient's diet, can thus be tested for compatibility or reaction. Actually, in the majority of instances the order of probability of sensitization which has been worked out by Rinkel et al[3] is found to apply to most patients in our practice.

The interpretation of these tests is dependent upon the acuity and experience of the allergist in evaluating the clinical response. In general, a rapid, severe and prolonged reaction indicates a high degree of sensitization. A doubling of the incidence of nasal symptoms in the postprandial period is significant, and the tested food should be considered an allergen. It is important to remember that a negative or compatible reaction to a test food establishes compatibility to that food only in terms of its immediate previous incidence in the diet.

If, after a complete food study, only one to a few foods have been found to be reactors, the patient can be placed on a restrictive diet eliminating those foods completely. This is the therapeutic test and the patient should be cleared of his perennial nasal symptoms due to food sensitization. Later on, when the allergenic food has become compatible by avoidance, the interval of usage can be determined.

If the patient has reacted to a large number of foods, he is considered to have a "low inherent tolerance to foods" and is placed on a rotation diet as described by Rinkel et al.[3]

The briefly described diagnostic methods have been the most satisfac-

tory that we have been able to work out for our own practice. Their use has resulted in a clinical impression that a causal diagnosis of food sensitization in perennial nasal allergy can be made in at least twenty-five per cent of the cases.

CASE REPORT

These cases are presented to illustrate several typical histories and responses to food testing which resulted in relieving patients of chronic allergic rhinitis of several years' duration.

Case 1.—Mrs. D. M., age forty-four, complained in November, 1953, of recurring attacks of severe nasal obstruction, watery nasal drainage, thicker mucoid postnasal discharge, and bilateral frontal and maxillary sinus region pains. No relationship to season or environment could be established, and symptoms lasted from weeks to months, with symptom-free intervals of only days to a few weeks. To us the history suggested a possible food sensitivity and the patient was started on individual food testing. Corn, wheat, egg, milk, beef, white potatoes, oranges and apples gave no reaction. Within five to ten minutes after the initial coffee feeding, severe nasal blocking occurred, followed by profuse watery nasal discharge and severe nausea. The severe symptoms persisted for three hours and because the patient experienced such general malaise the second feeding was omitted. Chocolate produced a similar but a less severe reaction. Since the results of specific feeding tests revealed only the two important food reactors, this high inherent tolerance permitted management by restrictive diet with complete coffee and chocolate omission, and advice that her substitute beverages be more diversified and rotated in their usage.

The patient obtained complete relief from nasal symptoms until October, 1954, when a severe sore throat with fever was followed by persistent nasal blocking, thick nasal secretion, and frontal headache. A left maxillary sinusitis was found and cleared on antrum irrigations and Proetz displacements. Persistence of nasal symptoms led to further allergic workups and, after food re-evaluation failed to reveal any new sensitivities, house dust was tested and the patient finally responded to very dilute dust hyposensitization with complete relief of symptoms, and it has been found necessary to continue this maintenance dust till the present time.

Case 2.—Mr. H.F., age thirty-nine, complained in May, 1950, of a persistent "sinus condition" with pronounced nasal stuffiness and thick mucoid postnasal discharge which had been present for over ten years. The symptoms had not been previously relieved by many local nasal treatments. The patient had been skin tested, but the subsequent trial on allergic management had failed, so the patient had given this up. Since the symptoms persisted all year and had not been relieved by trips to Arizona, New Mexico and California, food sensitization was suspected. The only reaction from individual food tests was to corn. Within ten minutes after the first feeding, sneezing and watery nasal discharge began and was followed by severe nasal blocking which lasted the rest of the afternoon. About three and one-half hours after the first feeding the patient experienced dyspnea, palpitation and a persistent, dull generalized headache. The alarming symptoms resulted in an electrocardiogram which showed some abnormalities which were absent on tracings repeated the next two days when the symptoms had disappeared. Because of this unusual reaction, a second corn test feeding was advised one week later, and under observation profuse watery nasal discharge began after the fourth spoonful of cornmeal mush. The feeding test was stopped because of the patient's apprehension, but the patient was convinced of his food sensitivity after having been very skeptical

because of the previous trial of allergic management based upon the skin testing diagnostic technique. Corn omission has resulted in complete relief, except when the patient inadvertently has a corn contact in the diet.

Case 3.—L.B., age ten, in February, 1950, was seen because of constant, but fluctuating nasal symptoms of stuffiness, thick nasal secretion and postnasal discharge which had not responded to "sinus treatments," penicillin, aureomycin or Benadryl®. Since September, 1949, the patient had been experiencing drowsiness around 3:00 p.m. daily, followed by a temperature elevation to 100° to 102° beginning around 4:00 p.m. Frequent attacks of abdominal pain, diarrhea, neck pain, joint pains, and weight loss, in addition to the other symptoms, had resulted in the variable pediatric diagnoses of suspect poliomyelitis, rheumatic fever and "liver disease," with resultant periods of hospitalization and bed rest at home but with no improvement in the nose or systemic symptoms.

A trial on dust hyposensitization gave only partial relief of nasal symptoms. A basic elimination diet showed marked generalized improvement by the fourth day, and subsequent individual food tests established milk as the food offender responsible for many of the nasal symptoms as well as the many systemic symptoms. Further allergic management by complete milk omission, house dust and *alternaria* hyposensitization resulted in the relief of nasal and constitutional symptoms, weight gain and a very dramatic improvement in behavior and personality noted by the physician, the parents and the child's schoolmates.

CONCLUSIONS

Food sensitization is an important cause of perennial nasal allergy, being an important factor in approximately twenty-five per cent of the cases of this common allergic disease seen in our practice.

Specific diagnosis of a food allergy depends upon demonstrating a cause and effect relationship between eating a given food and the production or increase of specific nasal symptoms. Such a demonstration of cause and effect to the patient establishes a sound basis for subsequent dietary omission and subsequent relief of nasal symptoms.

Cases of perennial nasal allergy responding partially on inhalant hyposensitization should always be studied for a possible complicating food allergy.

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55 East Washington Street

SOUTHWEST ALLERGY FORUM

The 1956 meeting of the Southwest Allergy Forum will be held at the Hotel Beaumont, Beaumont, Texas, April 1-3.

RETINAL DETACHMENT POSSIBLY DUE TO STRESS, PARASYMPATHOTONIA, AND NON-ADAPTATION SYNDROMES

Report of a Case

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CORRELATING and evaluating the psychogenic overlay, the corticosteroid measurements, the Minnesota Multiphasic Personality Inventory Test, and the pathologist's report, when available, may eventually prevent many diagnoses of idiopathic diseases.

Today, in a large sense, the world has the "jitters." We see people even in high places "cracking" under the strain of life's demands. Campaigns and literature on cancer, poliomyelitis, and heart disease, wars and rumors of wars, as well as the emotional strain of our modern society and insecurity, raise the sensitivity level of our psychosomatic and allergic mechanism.

A person's temperament is a key to the disease which may afflict him. Possibly the most startling medical discovery of this generation is the fact that one's personality can literally kill him. Excess parasympathetic stimulation, parasympathotonia, which produces autonomic dysfunction, is but the neural manifestation of a more basic factor which may lie in the psyche and is the result of environmental situations, conscious or unconscious, commonly referred to as situational stress. A disordered hypothalamic response may underlie the condition. Emotion and stress are apparently transmitted from the psychomotor centers of the frontal lobe to the hypothalamus, a nuclear center for the central autonomic system.

Blumberg[4] states that corticosteroid measurements and the Minnesota Multiphasic Personality Inventory Test show a parallelism in several hundred cases of established cancer, indicating that the psychogenic overlay plays a definite role in the growth of malignancies.

This case of retinal detachment is presented to suggest that stress and/or allergy may produce the same pathologic picture as infection, trauma, metabolic disturbances, blood dyscrasias and atherosclerosis, and may help explain many of the diagnoses of so-called idiopathic disease made in the past. Stress is the sum total of life's situations which produce tension. Tensions caused by anger, anxiety, jealousy, fear and worry may produce vasospastic conditions resulting in smooth muscle spasm of the arterioles with capillary and venule dilatation, transudates, and anoxia, possibly ending with an obliterative arteritis. This process can occur rapidly, due to a sudden vasomotor storm, or can be due to prolonged abnormal physiologic trauma. It is due to two factors: (1) stress,

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whether of psychic or somatic nature, and (2) reaction pattern, or predisposition to intrinsic as well as extrinsic environment, with which the subject is endowed. Stress is the "trigger mechanism" and the reaction pattern determines the location, character, and intensity of the expression. The reaction pattern may involve any organ throughout the entire body. Stress and allergy often go hand in hand, and many times allergic phenomena occur only during exceptional periods of stress. Stress may cause tension headaches, histamine cephalalgia, angioneurotic edema, conjunctivitis, iritis, glaucoma, retrobulbar neuritis, spastic angioretinopathy, detachment of the retina, Ménière's syndrome, asthma, angina, peptic ulcers, hypermotility, gastritis, mucous and ulcerative colitis, gallbladder involvement, and appendicitis, as well as dermatitis of various kinds.

Wolff[26] shows how the impact of man on man may be as seriously traumatic as the assaults of micro-organisms, climate, chemical, and physical forces. Disruptions, hindrances, and threats stemming from the inner action of man on man, both singly and in groups, evoke adaptive responses indistinguishable from those set off by other environmental forces. It becomes evident that failure to appreciate the significance of threats of deprivation of basic needs and of the opportunity to fulfill potentialities makes impossible an understanding of disease in man.

Read[16] states, "For my own part, after thirty years of close association with physical and mental derangements of health, I am persuaded without a shadow of doubt, that with the exception of unforeseen accident, the origin of every form of disease, both surgical and medical, whether hereditary or not, can be traced by careful investigation to the influence of fear upon the human mechanism."

Studies by Stevenson,[21] Rudolf and Ashby,[17] Lewis,[10] Moore, [11] Pollack,[12] White,[23] and Bacon et al[2] all suggest that long standing and tense emotional stress may exert a profoundly stimulating effect on the growth rate of an established cancer in man, as well as other pathologic syndromes.

Hansel[6] emphasized that the psychosomatic state of the patient might be caused by allergy, producing cerebral edema with its many manifestations. The dysfunction of the autonomic nervous system, as mentioned by Williams,[24] and the vascular basis of allergy of the eye as proposed by Duggan,[5] as well as Hilger's[8] papers, accentuate the part played by emotions and allergy.

Kos,[9] in a recent paper on Ménière's syndrome, pertaining to cases he had followed for eight years, considers the pathology is on a psychosomatic basis, as medical therapy of all kinds had failed. Evaluating the situation to the patient gives him an insight into his condition, oftentimes proving of more value than any chemotherapy, antibiotics, or other form of medicinal therapy.

Two excellent examples of retrobulbar neuritis caused by food allergy were reported by Allen and Seidelmann[1] and Rathgeber,[15] and clinically proven by a repeat performance when the foods were eaten. Ruedemann[18]

mentions a young man who experienced four retinal detachments in one year due to chocolate. The author[13,14] reported in 1954 several cases of retrobulbar neuritis due to emotional stress and fatigue, as well as one case of retinal detachment due to vitamin sensitivity in 1937.

Emotions often play a large part in glaucoma and may be the dominating factor in specific cases, causing detachment of the retina. Berans[3] and Wiseman and Moore [25] report glaucoma due to food sensitivity. Harrington[7] states that psychic trauma in a susceptible individual can produce as profound organic change in the eye as extreme anoxemia or direct physical trauma. He states the increased wartime incidence of certain disturbances of autonomic origin can be explained in no other way. Many cases of amaurosis fugax and central spastic angioretinopathy have been definitely established to be due to vasomotor instability and vasospastic etiology of the retinal lesion. There are perhaps few places in the body so well adapted to the clinical study of such phenomena as the eye, much of whose normal physiology is under autonomic control.

When pathologically involved,[20] the retina splits within itself, separating into two layers. The outer layer, a pigment epithelium, remains adherent to the choroid, while all the other layers are lifted from the pigment epithelium by a serous exudate. Other causes[28] are accumulation of subretinal fluid, allergy, hemorrhage, trauma, edema, disinsertion, cystic degeneration, neoplasm, cysts, myopia, choroiditis transudates, detachment of the vitreous, holes in the retina, distention, depression, exudates of an inflammatory process, hypotiny, contraction of the vitreous, retinitis proliferans, Drusen on Bruchs membrane,[27] ossification of the choroid, retinal venous occlusion, hypertensive retinopathy, and adhesion between retina and vitreous.

CASE REPORT

The patient, a white man, aged fifty-two, who is the manager of a large department store, had a fire in his business establishment. He stated that he was in the basement trying to get out papers during the fire, that he inhaled some smoke but was not overcome. A few minutes after the fire, he noticed that he had difficulty in seeing with his left eye. This difficulty continued, and a week later he consulted an optometrist, who told him that he ought to see an opthalmologist as he believed he had some serious difficulty. He waited another week, so two weeks elapsed after the fire before he sought medical help, and at that time he had a complete detachment of the upper half of his left retina and his central vision was practically occluded. No tears could be seen in the detachment, nor could any history of trauma, myopia, hypertension, iritis, uveitis, malignancy or multiple causes of detachment be elicited. Transilluminations showed no area of increased density suggesting a malignancy. Previous to this episode, vision had been good in both eyes. Past medical history consists of many bouts of gastritis, stomach ulcers, pylorospasm, intestinal hypermotility, and one heart attack for which he was hospitalized. He is very allergic to cheese. He is an extremely nervous individual, carrying on a highly competitive chain store business, living and thinking business day and night. He has a lot of drive and does not seek medical attention when ill unless it is absolutely necessary. He had had this history of ulcer and gastric complaints for several years and has had medical treatment on many occasions. He continues to take large doses of alkalies daily to control the pain.

Surgery was performed to correct the retinal detachment. On the first postoperative day the patient was under so much apprehension, in spite of large doses of sedatives, that he vomited continuously and had severe pains in his heart and stomach. Binocular dressings were an impossibility because of his fear and apprehension. On the second and third days he developed a complete ileus, and for the next five days, in spite of excellent medical consultation, it was doubtful whether he would survive. For two days he was completely delirious, semi-conscious, and disoriented, and was kept in bed only with much difficulty. His cardiac and gastric complaints were quite severe; his apprehension and nervous instability were marked features of his postoperative convalescence. He was finally discharged from the hospital with only a portion of the detached retina remaining in place. He was checked for several weeks, and the question of further surgery arose. Because of his multitude of psychosomatic complaints, situational stress, vagotonia, and his instability, more surgery was contraindicated. He was seen at a university and at two other large clinics and was advised against further surgical procedures. At the present time he is back in business, his eye is causing him no special difficulty, and he is continuing his ulcer therapy.

ADDENDUM

This patient, one month ago, while on the train to St. Louis on a buying trip, was removed from the train and died one hour later. This may further accentuate the vagotonic condition of this patient's nervous mechanism, as he died of a heart attack.

SUMMARY

Psychic trauma in a susceptible individual may produce as profound an organic change in the eye as extreme anoxemia, direct physical trauma, allergy and perhaps many of the multitude of pathologic causes of retinal detachment.

The patient whose history is presented is, psychically, a very susceptible individual, as indicated by his extremely stormy postoperative course, his long history of ulcer and cardiac attacks, and sudden possible retrobulbar neuritis, followed by detachment of the retina.

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207 East 2nd Street

PENNSYLVANIA ALLERGY ASSOCIATION

At a meeting of the Pennsylvania Allergy Association held at Hotel William Penn in Pittsburgh on September 21, 1955, the following officers were elected for the year 1956:

President.....Lester L. Bartlett, M.D., Pittsburgh

President-Elect.....James Flood, M.D., Sayre

Secretary-Treasurer.....Ralph Mulligan, M.D., Reading

Board of Regents.....Charles Cleland, M.D., Kane
Jean Crump, M.D., Philadelphia

The spring meeting of the Association will be held at Galen Hall, Wernersville, Pennsylvania, May 17-20, 1956.

INDUSTRIAL DERMATITIS

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A DISCUSSION of the relationship between industry and medicine should show the increasing responsibility of the medical profession not only to disease of the individual but also to his economic and industrial position in society relating to the disease. This is especially important in the southeastern part of the United States because there is and will continue to be an increasing industrialization of this area. Already, both labor and management are complaining of the lack of trained and interested doctors who can evaluate properly and care for industrial disease in this area.

An exchange of experiences is essential between specialty groups, as well as communication with the general public, executives of industry, and labor groups, about industrial diseases, their inception, and prognosis.

The terms and criteria regarding the industrial character of skin eruptions must be clearly understood by physicians, the worker-patient, the lawyers, management and labor, the insurance companies, and governmental agencies, all of which may participate in some way in the evaluation of a particular industrial dermatitis. This may seem all but impossible; it sometimes is.

First, let us distinguish between the terms "industrial accident" and "occupational disease." Much that happens to the patient will depend upon this distinction. By "industrial accident" is usually meant an event which takes place fortuitously and suddenly at a fixed time and without one's foresight or expectation—such as a broken leg or injury from a falling object.[1] An "occupational disease" is usually construed as one which results from the nature of employment. By nature is meant not only those conditions brought about by failure of the employer to create a safe place in which to work, but also those conditions to which all employes of a class are subject and which produce the disease as a natural incident of a particular occupation.[1] A distinguishing feature between the two is found in the fact that an industrial accident connotes suddenness as a cause, while an occupational disease requires time for its inception. We are herein primarily concerned with occupational disease, particularly with occupational diseases of the skin, and not with industrial accidents.

First, and foremost, the patient is interested in what his skin eruption may be, because he wishes to get well, stay well, and keep his job. Second, industry, both management and labor, is interested in keeping the employe as a worker and as a producer. Third, the insurance company is

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interested in the determination of its responsibility in the payment of compensation. And, finally, we, the physicians, are interested in the solution of a problem which has been placed in our hands.

An industrial dermatitis is any inflammatory disease of the skin in which occupational exposure can be shown to be a major causal, contributory, or eliciting factor.[3] There must be proof that this eruption is of industrial nature. For the physician, proof of the industrial nature of a dermatitis must depend entirely upon medical, and not legal, considerations. From the medical point of view, proof cannot be absolute of the *wholly* industrial nature in any given case, but there are certain medical criteria which indicate with a high degree of probability that the eruption in question is or is not industrial or occupational in origin. It becomes, then, a matter of medical opinion based on observable facts. What are these facts?

The criteria of the first order are: (1) Inception of the eruption. When? Where? How? (2) Amelioration of the eruption by cessation of work. (3) Recurrence of the eruption on return to work.

The criteria of the second order are:

1. Eruption occurs first in, and is confined to, maximum areas of exposure.

2. Character and localization conform to the character and localization of an eruption of nonindustrial hazard.

3. Application of casual agencies by properly applied patch test produces a similar reaction to that of the dermatitis.

4. Other workers are similarly affected.

5. Eruption appears soon after work begins on a new potential hazard.

6. The eruption can be shown to be of the type which may result from industrial exposure sustained. It must be shown that the eruption is not of nonindustrial nature, such as psoriasis or lichen planus.

It is at precisely this point in the observation of the supposed industrial dermatitis when half truths can be mistaken for whole truths. Here one must exercise his best dermatologic experience and judgment to make a clinical appraisal and a working diagnosis of the eruptions, so that he will not fall into an error of assumption—an assumption that because the eruption occurs in an employe of industry that the industrial exposure caused the eruption.

There are some common causes of erroneous conclusions that a given skin eruption is, or is not, of industrial causation:

1. It is wrongly considered as industrial in nature because the industry is notorious for the occurrence of a dermatitis.

2. It is wrongly considered of industrial nature because of a positive patch test to the substances contacted in industry.

3. It is wrongly considered of an industrial nature because it is accompanied by the finding of fungi or other microorganisms.

4. It is not considered industrial in nature because of negative patch tests.

5. It is not considered of an industrial nature because it is accompanied by positive tests to fungal or bacterial extracts.

6. It is considered to be of industrial nature because the worker is an allergic individual.

7. It is not considered an industrial dermatitis because it did not clear up when the patient ceased his work or during a vacation.

There are numerous predisposing factors which may and do set the stage for the development of an industrial dermatitis—factors such as race, type of skin, sweating, age, sex, season of the year, cleanliness, and other existing skin diseases. But the factor in which we are most interested is that of allergy.

It seems essential that we again define our terms. For the purpose of our present discussion let us define allergic dermatitis as an altered reactivity caused by a first contact with a substance, and manifested after an interval of time (period of incubation) by contact with the original or identical substance. The dermatologist is more likely to label this as "hypersensitivity," in order that he may use the opposite term, "hyposensitivity." This, in order to describe a lessening of the allergy, since he has observed that the phenomenon is a two-edged sword." He, therefore, speaks of two types of skin eruption, those caused by primary cutaneous irritants and those eruptions caused by cutaneous sensitizers.

Industrial dermatitis may then be produced by direct action of a chemical on the normal skin at the site of contact, if applied in sufficient intensity or quantity, as by a primary irritant; or industrial dermatitis may be produced by an agent which, on first contact, produces no demonstrable change, but on later and further contact, produces an eruption at the site or in distant portions of the skin, as by a skin sensitization. A primary irritant may be a sensitizing agent, but it should not be spoken of as allergenic until the sensitization action can be demonstrated. Often the seeming allergenic dermatosis can be explained by other factors of contact or irritation which occur and confuse the appearance, such as changing occupations, humidity, and changing home conditions.

Thus, the industrial dermatitis must be considered in the sum total of the mechanical, physical, and chemical action of all substances which may contact the skin of the worker.

While the fact that there is a specific hypersensitivity, both static and acquired, cannot be denied, many surveys in industry and in the public health service show that the allergic individual is not more liable to industrial dermatitis than is his nonallergic brother. That hypersensitivity

can be acquired, and that it can be deliberately produced, is a fact in industrial experience. It is also an observed fact that certain individuals upon repeated contact may develop a dermatitis, but can by repetition of this contact become hyposensitive, or, as the workers label it, can be "hardened" to their occupation. Sensitivity does work both ways.

TABLE I

Petroleum products and greases caused	11.7%
*Plants	10.7%
Alkalis and their compounds	10.2%
Solvents (and other mineral oils)	9.2%
Metals and metal plating	8 %
Chromates and chromic acid	5.2%
Dusts	4.8%
*Dyes and dye intermediates (fur dyes not included)	4.3%
Chemicals, unspecified	4.2%
Acid and acid fumes	3.4%
*Rubber and its compounds	2.8%
Building cement and concrete	2.5%
Paints, enamels, and varnishes	2.2%
*Resins	1.8%
Burns and physical agents	1.6%
Biologic agents	1.2%
Cyanides	1.1%
*Coal tar products	1.1%
Desiccators	0.6%
Non-metallic elements	0.6%
Oils, vegetable (oils, fats, and waxes)	0.4%
Halogens and their derivatives	0.2%
*Miscellaneous	1.3%
Unknown	9.8%

*Allergenic substances likely to be found.

The large majority of cases of occupational dermatitis are due to the primary irritants, and only a small percentage are due to sensitizing agents or allergy. In a compilation of 10,000 patients with occupational dermatitis reported by various state boards of compensation prior to 1939, 80 per cent were listed as having been caused by primary irritants or infection. Allergenic substances, as such, like plants, dyes, rubber, et cetera, cased only 20 per cent. This is illustrated in Table I. The groups of substances marked with an asterisk are ones in which allergenic substances are likely to be found.[2]

This is not the case, however, among the wearers of finished materials. Here allergy is the most frequent cause of skin eruptions, as shown by the fact that most finished products are harmless to the vast majority of the population.[2]

How will we work our way through this maze of uncertainties, complicated factors, and the many methods involved, in order to discover the true facts in a given case? It is much like solving a murder mystery, and in many instances the physician must be a veritable Sherlock Holmes in order to arrive at a proper conclusion. However, we must not fall into the common error that the mere solving of the central problem, as is done in detective stories, settles the case. The patient remains with his eruption and has to be cared for. His family and the insurance company, as well as the patient, must have a prognosis; his employer must understand when and how and where he can return to work. The mere "solution" of the

problem is not sufficient. It frequently brings only more questions to be answered.

Good dermatologic treatment must be given until complete relief of signs and symptoms can be accomplished. This is not infrequently time consuming and expensive, and can be obtained only with the co-operation of the patient with a desire to get well. Protection from known irritants upon return to work, either by changing the method of work or by changing occupation, is essential. This requires an intimate knowledge of the working conditions, and can best be handled by the industrial physicians.

It would then seem obvious that the facts must be known to the physician, to the employer, to the employe, and to the insurance carriers, in order that the conditions confronting them all can be equitably settled. It is not enough, therefore, for physicians to decide merely upon cause and effect. They must, in addition, be prepared to relieve, change, and remove those causes and effects.

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AIR POLLUTION RESEARCH

The U. S. Public Health Service, on the recommendation of the National Advisory Health Council, has awarded ten grants totaling $295,367 for research into air pollution problems. Of this amount, $69,209 will go to Dr. John J. Phair at the University of Cincinnati for a study to relate the incidence, prevalence, and prognosis of human disease to air pollution in an urban area. Drs. E. Wendell Hewson and John M. Sheldon at the University of Michigan will receive $63,420 for a study of atmospheric pollution by aeroallergens, and $43,107 will go to the Utah State Agricultural College where Drs. Delbert A. Greenwood and Richard H. Call will study the effect of atmospheric fluorides on man. Approximately $205,000 remains in the congressional appropriation for future study in this field.

A CLINICAL STUDY OF PREDNISONE IN SEVERE INTRACTABLE BRONCHIAL ASTHMA

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THE administration of corticotropin (ACTH), cortisone and/or hydrocortisone has become recognized as an effective means for the relief and control of the symptoms of status asthmaticus and severe persistent asthma.

Although the symptoms returned in variable short periods after the discontinuance of these drugs in the perennial type of bronchial asthma, these agents were effective in most cases if they could be employed continuously without serious side effects at the optimum maintenance level. We agree with Brown[1] whose examination of the literature in 1954 showed that 85 to 95 per cent of patients selected with care derived immediate and striking symptomatic improvement from these corticosteroids. However, the constant need for a maintenance dose (often at high levels) in the otherwise problem cases of chronic asthma of undetermined etiology, and those refractory to routine antiasthmatic drug therapy and hyposensitization, has led to undesirable side effects of hypercorticism with altered physiology and chemical imbalance.

Fortunately, sodium restriction and potassium supplementation will prevent many undesirable states attributable to abnormal levels of the electrolytes but such multiple therapy is often difficult to pursue in patients not under daily clinical observation and supervision.

We are concerned primarily in establishing an etiologic diagnosis in bronchial asthma and instituting early specific hyposensitization and/or removing the offending agent. Most cases can be adequately controlled by these procedures. However, until the advent of steroid therapy, there was a problem group that resisted the well-formulated procedures in the antiallergic program as the response to these measures was unsatisfactory and incomplete.

The need for a drug for the symptomatic control of problem cases of chronic bronchial asthma which failed to respond to the conventional forms of therapy led to a constant search for agents of more effective long-term control and decreased undesirable side effects.

In this study we accepted and tabulated the subjective complaints, but we were concerned chiefly with undesirable objective findings and their possible elimination in patients previously treated with ACTH, cortisone and/or hydrocortisone.

The promise prednisone held for chronic asthmatic patients, because of its favorable effects in low doses and infrequent side effects in rheuma-

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toid arthritics as reported by Bunim, Pechet and Bollet[2], prompted this clinical study.

Prednisone* is described as a highly potent crystalline corticosteroid or cortisone-like steroid with marked antirheumatic and anti-inflammatory properties. The structural formula differs from cortisone by the presence of a double bond between C_1 and C_2 produced by dehydrogenation at positions one and two of the cortisone nucleus. Its structural relationship to cortisone and hydrocortisone is shown in Figure 1.

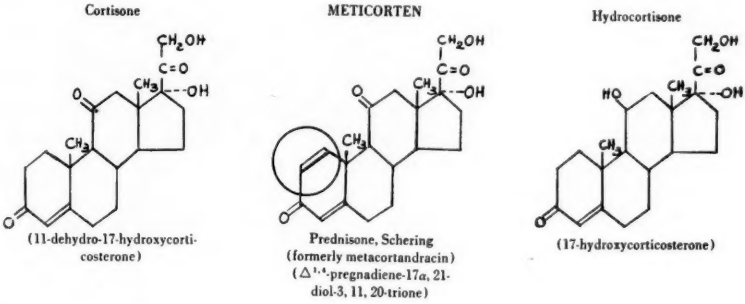

Fig. 1.

The drug is prepared in a compressed tablet form of 5 mg each for oral administration and scored to facilitate the use of smaller doses.

SELECTION OF PATIENTS

The group selected for this study consisted of thirteen patients (seven females and six males) varying in age from eighteen to sixty-eight years. The following criteria were used in selecting the patients: (1) a history of persistent perennial asthma of more than two years' duration; (2) patients who were known to the author for one year or longer either in the clinic or in the office; (3) patients who had been studied previously and had received routine antiasthmatic therapy including hyposensitization but remained resistant to treatment with continuous wheezing and dyspnea until placed on steroid therapy; (4) patients in whom numerous diagnostic procedures had failed to establish a specific etiologic diagnosis; and (5) patients who had previously received steroid therapy (ACTH, cortisone and/or hydrocortisone) with a satisfactory suppression of asthmatic symptoms and a sense of well being but had developed objectionable side effects when the maintenance doses, with frequent necessary increments, were continued over long periods.

*Prednisone (formerly known as metacortandracin) used in this study is a synthetic steroid manufactured and distributed by the Schering Corporation, Bloomfield, New Jersey, and is marketed under their brand name, Meticorten®.

None of the patients in this group had a history or findings of psychoses, gastrointestinal bleeding, tuberculosis, diabetes or congestive heart failure.

TABLE I. PREVIOUSLY OBSERVED OBJECTIONABLE SIDE EFFECTS

1. Retention of sodium and fluid—12 patients.
2. Weight gain—12 patients.
3. Cervicodorsal hump (buffalo hump)—1 patient.
4. Increased level of blood sugar—6 patients.
5. Temporary glycosuria—6 patients.
6. Amenorrhea (intermittent)—3 patients.
7. Hirsutism—3 patients.
8. Acne—6 patients.
9. Slight demineralization of lumbar vertebra (L_3)—1 patient.
10. Epigastric distress—2 patients.
11. Hypertension—4 patients.
12. Moon face—3 patients.

The objectionable features listed above occurred on ACTH, cortisone or hydrocortisone. In three patients the three drugs were employed successively in an attempt to eliminate undesirable side effects without success.

Four months before this study began one of the patients (E. W.) developed erythema nodosum lesions, tender erythematous nodules symmetrically located on the extensor surfaces of the legs without ulceration, and angioneurotic edema of the lips and eyelids with marked edema of the tongue before steroid therapy. A sensitivity to iodide was suspected as the patient was receiving potassium iodide 0.3 gm three times daily as an expectorant in addition to bronchodilators. The drug was discontinued and cortisone therapy and a sodium restricted diet were instituted with supplemental potassium chloride 10 grs three times daily. The lesions cleared within eight days with disappearance of wheezing and dyspnea. Three weeks later edema became manifest with symptoms of drowsiness, fatigue, loss of appetite and generalized muscular weakness. Careful questioning and a complete reinvestigation revealed that, two days after the supplementation of potassium chloride, the patient discontinued this medication because of nausea and diarrhea, and returned to a nonrestricted diet without the knowledge and permission of the physician. The electrocardiogram showed a depression of the S-T segment, lowered T waves and a lengthened Q-T interval indicating hypopotassemia. This case stresses the need for frequent observation and direct supervision by the physician of patients receiving steroid therapy.

METHOD OF STUDY

This study dealt with the use of prednisone in thirteen patients (seven females and six males) who were known to us for one or more years. These patients had received steroid therapy for three to twenty months prior to this study and although they had received satisfactory, and frequently complete, relief of the symptoms of asthma they were willing to participate and co-operate in these clinical trials because of their concern about the objectionable side effects of the previously administered steroids.

Before beginning the clinical study with prednisone each patient received

roentgenographic examination for other possible intrathoracic disorders, and determinations were made of blood counts, blood pressures, vital capacities, fasting blood sugar, serum sodium and potassium.

The maintenance doses of the previous steroids were gradually reduced by one-third to one-half each day with the hope of complete elimination by the third day. The patients were given routine antiasthmatic treatment similar to the regimen suggested by Burrage and his group[3,4] in the study of cortisone in severe asthma, with the exception that intravenous fluids other than aminophyllin were not administered. We felt that the presence of obvious edema in most of the patients and the need for determinations of fasting blood sugar, serum potassium and sodium levels early in the study obviated the use of venous infusions of glucose and electrolytes, as these agents might alter the blood level values. Aminophyllin was given intravenously twice a day, or oftener if needed, to prevent the sudden and alarming return of severe wheezing. The symptoms of asthma returned within twenty-four to seventy-two hours. The presence of wheezing and dyspnea permitted us to determine the initial dose of prednisone required for the suppression of symptoms.

Each patient was placed on a normal diet without sodium restriction or potassium supplementation, as Bunim and his group[2] had reported there was no sodium retention nor excessive potassium excretion with this drug. The caloric and protein intake was adjusted to the patient's needs. We insisted upon a minimum of 1 gm of protein for each kg of body weight.

The patients were seen at four-day intervals for blood pressure readings, weight determinations, chest examinations and inquiries as to symptoms. Laboratory studies for urinary sugar, serum sodium and potassium were made at four-week intervals. Urinary excretion of 17-ketosteroids and absolute counts of circulating eosinophils were determined before and after prednisone therapy. Vital capacity determinations were made immediately before and at the end of clinical trials. Hyposensitization with indicated inhalants was continued at three-week intervals throughout the trials, which extended over a period of eleven to fifteen weeks (Tables II and III).

DOSAGE

As no standardized or accepted range of dosage was available for the treatment of chronic bronchial asthma at the beginning of this study, we selected a dosage which we felt would be adequate to terminate or suppress completely the signs and symptoms of asthma and reach a maintenance dose without producing untoward symptoms or objectionable side effects. The following dosage schedule was employed with occasional variation according to individual response.

The initial dose was 40 mg (10 mg every six hours) the first day; 30 mg for two days (7½ mg every six hours) or until the symptoms were

TABLE II. CLINICAL OBSERVATIONS IN PREDNISONE THERAPY OF ASTHMA

Name	Age	Sex	Previous Steroid Therapy	Initial Daily Dose	Maint. Dose Daily	Duration of Treatment (weeks)	Weight Before Treat. (lbs.)	Weight 8 Days After Treat. (lbs.)	Blood Pressure		Vital Capacity		
									Before Treat.	After Treat.	Before Treat.	After Treat.	Increase
S.G.	55	M	ACTH Cortisone Hydrocort.	40 mg	15 mg	15	187	182	168/86	160/84	2900 cc	3800 cc	900 cc
E.W.	31	F	Cortisone	40 mg	10 mg	15	156	154½	114/72	114/72	2800 cc	3900 cc	1100 cc
K.P.	61	M	ACTH Cortisone	40 mg	20 mg	12	189	184	174/106	158/100	1500 cc	3200 cc	1700 cc
M.S.	43	F	ACTH Cortisone Hydrocort.	30 mg	10 mg	11	155	150	118/76	114/72	2400 cc	3600 cc	1200 cc
S.T.	18	F	Cortisone	40 mg	5 mg	14	128	127	110/72	110/70	1700 cc	3500 cc	1800 cc
W.B.	54	M	Cortisone	40 mg	10 mg	15	189	185	172/100	162/94	2100 cc	3700 cc	1600 cc
G.T.	68	F	ACTH Cortisone	30 mg	10 mg	11	163	159½	166/94	158/88	2400 cc	3500 cc	1100 cc
J.W.	27	M	Cortisone Hydrocort.	40 mg	10 mg	15	163	158	134/76	128/72	1900 cc	4000 cc	2100 cc
L.J.	45	M	Cortisone Hydrocort.	40 mg	10 mg	14	190	186	144/86	140/82	2100 cc	3300 cc	1200 cc
E.J.	46	F	Cortisone	40 mg	10 mg	13	156½	153	138/78	132/74	2300 cc	3700 cc	1400 cc
M.D.	61	F	Cortisone Hydrocort.	40 mg	15 mg	13	152	147½	140/82	136/76	2600 cc	3600 cc	1000 cc
A.B.	38	M	Cortisone Hydrocort.	40 mg	5 mg	15	149½	147½	128/72	122/70	2300 cc	4200 cc	1900 cc
T.T.	32	F	ACTH Cortisone Hydrocort.	40 mg	10 mg	14	154½	151	120/74	120/72	2100 cc	3500 cc	1400 cc

completely suppressed. The daily dosage was then reduced in a gradual step-like fashion by 5 mg every fourth day, until a maintenance dose was reached. This level was determined as the dosage just above that which permitted a recurrence of symptoms. The daily maintenance dose in this series was usually 10 mg (5 mg after breakfast and the evening meal), but varied from 5 to 20 mg (5 mg in two cases; 10 mg in eight cases; 15 mg in two cases, and 20 mg in one case). If symptoms recurred the dose was raised by increments of 5 mg daily until an adequate maintenance level was established. Marked clinical improvement was observed within twelve to forty-eight hours, with a significant decrease in asthmatic symptoms resulting from respiratory embarrassment. Patients in this clinical study received prednisone treatment for eleven to fifteen weeks. The two patients studied for eleven weeks were placed on an initial daily dose of 30 mg (instead of the 40 mg previously employed) which was continued for three days. The clinical response was satisfactory; however, the onset of subjective improvement and the complete suppression of symptoms were less rapid with the reduced initial dose. In two cases of intercurrent infection with purulent sputum, a broad spectrum antibiotic was used concurrently with the prednisone.

RESULTS AND DISCUSSION

This series of thirteen patients represents cases of severe intractable bronchial asthma of the perennial type who received only mild to moderate relief with bronchodilator drugs, expectorants and hyposensitization. One

TABLE III. LABORATORY FINDINGS AND SIDE EFFECTS IN PREDNISONE THERAPY IN BRONCHIAL ASTHMA

Name	Reduction in 17-ketosteroid excretion	Reduction in Eosinophils	Serum Sodium mEq/1		Serum Potassium mEq/1		Objectionable Features	
			Before	After	Before	After	Before Prednisone	After Prednisone
S.G.	11.1 to 6.1 mg	480 to 108	148	140	4.0	4.5	Edema, weight gain, acne	Insomnia
E.W.	10.2 to 5.3 mg	880 to 210	146	143	4.0	4.1	Edema, weight gain, increased blood sugar, intermittent amenorrhea, hirsutism	Increased appetite
K.P.	11.2 to 5.6 mg	420 to 104	148	138	3.8	4.2	Edema, weight gain, headache, glycosuria, cervicodorsal hump	Increased appetite
M.S.	9.5 to 4.8 mg	680 to 75	148	139	4.0	4.3	Edema, weight gain, hirsutism, increased blood sugar, acne, moon face	Increased appetite, insomnia, palmar perspiration
S.T.	9.8 to 4.7 mg	460 to 2	148	143	4.1	4.2	Edema, weight gain, acne, intermittent amenorrhea, glycosuria, epigastric distress	Epigastric distress
W.B.	11.2 to 6.0 mg	412 to 84	145	140	4.0	4.3	Edema, weight gain, slight demineralization	Insomnia, increased appetite
G.T.	10.0 to 5.1 mg	274 to 28	147	143	4.1	4.2	Edema, weight gain, acne, increased blood sugar, glycosuria	Increased appetite
J.W.	11.4 to 5.8 mg	410 to 2	147	140	4.0	4.3	Edema, weight gain, epigastric distress	Epigastric distress
L.J.	11.4 to 5.3 mg	440 to 106	147	139	4.0	4.4	Weight gain, glycosuria, increased blood sugar, edema	Increased appetite
E.J.	9.4 to 4.8 mg	776 to 302	147	142	4.0	4.3	Edema, weight gain, acne, moon face, hirsutism	Increased appetite
M.D.	8.2 to 4.2 mg	482 to 26	148	141	3.9	4.5	Edema, weight gain, increased blood sugar, glycosuria	Insomnia
A.B.	9.8 to 4.5 mg	310 to 8	145	142	4.2	4.4	Increased blood sugar, glycosuria	Increased appetite
T.T.	9.1 to 4.0 mg	324 to 0	148	141	4.0	4.5	Edema, weight gain, acne, intermittent amenorrhea, moon face	Increased appetite

patient in this series (K.P.) had the complication of marked chronic pulmonary emphysema and pulmonary fibrosis with chest deformity.

Although eight patients showed a moderate to marked skin reaction to house dust and *alternaria,* and three patients to mixed feathers, with histories of repeated respiratory infection in seven cases, attempts at hyposensitization with these specific allergens and the use of antibiotics before starting steroid therapy produced only mild to moderate relief. We felt that the multiple sensitivities which existed (some of them probably as yet undetected), as well as the chronicity of respiratory disorders with resultant sequelae, rendered routine antiasthmatic therapy relatively ineffective.

Because of a cortisone-like effect of this drug we realized the need for arriving at the lowest level possible for maintenance compatible with the symptom-free state in order to avoid major undesirable side effects.

Vital capacity determinations were made before and after prednisone

therapy and showed an increase in each case after treatment, as shown in Table II. Each patient had a prolongation of expiration with wheezing, dyspnea and cough at the beginning of therapy. The signs and symptoms indicated a partial obstruction at least in many if not all of the lower air passages, thereby retarding the rate of air flow and causing a decreased maximum breathing capacity. We were cognizant of the value of the maximum breathing capacity test in patients with wheezing and dyspnea but, after observing the marked fatigue and the accentuation of dyspnea and wheezing in three of these patients with this test before therapy, we deemed it inadvisable to continue its use and therefore substituted the vital capacity test.

During the first four to eight days there was a weight loss in eleven patients of two to five pounds, which was only partially regained in seven patients without evidence of edema within twelve weeks. This initial weight loss is apparently due to an elimination of the previously retained sodium and fluid. The partial replacement of the fluid weight with increased body mass is most likely due to an increased appetite with a concomitant increase in caloric intake.

Serum sodium and potassium studies revealed an elevation or retention of sodium in ten patients and a reduction of potassium at the beginning of the trials, but a return to normal values was noted at the end of four weeks without restriction of sodium or the use of supplemental potassium. The absence of serum potassium deficit with the dosages employed implies that the damage to tissue cells and the cellular changes of the kidney necessary for the loss of nitrogen and potassium were not of the magnitude found with the older steroids.

We realize that the serum potassium level alone does not reflect at all times the concentration of intracellular potassium, as some patients severely depleted of intracellular potassium may have a serum potassium within normal range. However, in such cases, the signs and symptoms are suggestive of potassium deficit and the electrocardiogram will show abnormalities. If such symptoms are present, electrocardiographic tracings should be made, as was done in case E. W., who in error discontinued the potassium supplement while on cortisone therapy.

Two cases exhibited moderately purulent sputum during the trials which was controlled by the use of a broad spectrum antibiotic for five successive days.

The fasting blood sugar did not exceed the upper limit of normal, and glycosuria was not observed in any patient in our series while on prednisone; in fact, there was a reduction to normal range in the previously elevated blood sugar levels on steroid therapy prior to this study. This apparently implies a gluconeogenesis and a lowering of the renal threshold for glucose to a smaller extent than that observed with cortisone therapy adequate to control symptoms. Glucose tolerance studies were not done during this period of clinical observation.

Four patients in the group exhibited hypertension before treatment with prednisone, with two complaining of an increasing frequency of headache. After treatment there was no elevation of the previously existing blood pressure. Conversely, there was a reduction in ten of the former blood pressure levels. It has been our experience that as bronchospasm and edema are relieved in these patients there is a fall in blood pressure, unless the drug employed produces vasoconstriction and edema.

Vital capacities were determined immediately before and after trials with prednisone, and showed increases ranging from 900 to 2100 cc.

The previously employed steroids were withdrawn gradually until wheezing and dyspnea appeared, rather than suddenly or abruptly before beginning prednisone therapy. It has been our observation that severe symptoms of headache, nausea, nervousness, fatigue and depression immediately follow the sudden discontinuance of cortisone without the immediate return of asthma, which is usually delayed for days and occasionally for weeks.

The 17-ketosteroid excretion in the urine and absolute counts of circulating eosinophils were determined immediately before and after two days of prednisone therapy. The response to prednisone was similar to that shown to cortisone and hydrocortisone with a prompt suppression of 17-ketosteroid urinary excretion and a marked fall in the circulating eosinophils. Absolute eosinophil counts made at the end of eight hours in three patients, S. T., J. W., and T. T., revealed a more precipitous fall (Table III).

The significant fall in the 17-ketosteroid excretion would imply a cortisone-like action, as circulating prednisone inhibits ACTH production and the adrenal cortex is sensitive to a decrease in circulating endogenous ACTH. This means less stimulation of the adrenal cortex with less available 17-ketosteroids for urinary excretion.

The marked fall in circulating eosinophils may serve as a means of confirming adrenocortical function, but it alone would not suffice as definite proof of normal function, as it is quite variable in the degree of response and may be influenced by other factors operating in the body.

There was a regression of moon face at the end of eight weeks in two of three patients with this objectionable feature.

Two patients complained of epigastric distress with a slight burning sensation after receiving the drug for eight and twelve days, respectively. This distress was relieved by an antacid aluminum hydroxide gel. This relief suggests the possibility of excess acid production in some patients given this drug and may be the prelude to the production of gastric and duodenal ulcer. However, there was no radiologic evidence of crater formation or deformity of the duodenal bulb.

One patient (W. B.) complained of a dull backache in the lumbar region two weeks before this study. X-ray of the lumbar, thoracic, sacral and pelvic bones revealed slight demineralization in L_3. After determining

the urinary excretion of 17-ketosteroids in this patient, we administered sex hormones in combination following the suggestion of Jaros.[5] He states that the onset of the climacteric there is a lowering of both sex steroids, and in the patient with chronic asthma it has been found beneficial to replace the anabolic sex steroids by giving them in combination, which improves the asthma and tends to eliminate the complaints of backache in osteoporosis. Recent x-rays of the same region after twelve weeks of prednisone treatment failed to reveal further progression of the demineralization process.

UNDESIRABLE FEATURES

The objectionable features or side effects noted in this study were relatively mild or surely less severe and less frequent than those observed with previous steroid therapy. There was mild insomnia in four patients; epigastric distress in two; perspiration of palm of hands in one, and increased appetite in eight.

COMMENT

As these studies continue, we realize that we must always be alert to the possibility of peptic ulcer and of osteoporosis or demineralization in the weight-bearing regions in patients on prolonged therapy, especially in postmenopausal women and senile males. We must keep these patients on a well-balanced diet with adequate proteins and sufficient minerals particularly calcium. We must be prepared to institute estrogen and androgen therapy, as there is an estrogen lack and androgen deficit in elderly patients, which are responsible in a large measure for decreased osteoblastic activity and an inability to utilize calcium and retain essential phosphorus. This combined sex hormone therapy, along with the essential vitamins and minerals, tends to prevent impaired protein and calcium metabolism, with its consequent inadequate matrix and a negative calcium balance. We are also cognizant of the possibility of additional undesirable side effects resulting from the indiscriminate and prolonged use of cortisone-like drugs. These drugs may be life saving, particularly in emergencies, and their use is justifiable if we are aware of, and prepared to cope with, their potential hazards. Many of these possibilities may not arise if we attempt to control the symptoms of chronic asthma with the lowest possible dosages, in order to minimize the suppression of endogenous ACTH secretion and reduce nitrogen and potassium excretion.

We must continue to search for the etiologic agents and the statement of Brown[1] concerning the use of ACTH and cortisone may well apply here—"useful as these drugs are for symptomatic treatment, they have not in any way diminished the necessity for careful studies directed toward discovering the causative allergens."

SUMMARY AND CONCLUSIONS

1. Prednisone (Meticorten®) is a potent synthetic cortisone-like drug effective in the symptomatic treatment of chronic intractable asthma. It is effective in smaller initial and maintenance doses than cortisone or hydrocortisone with less frequent and less severe side effects.

2. The dosage required for symptomatic control of asthma was approximately one-third that of hydrocortisone and one-fifth that of cortisone.

3. Serum sodium and potassium and fasting blood sugar levels remained within normal limits with no glycosuria and there was no development of hypertension during the period of clinicial trials (eleven to fifteen weeks).

4. No retention of fluid was noted in our series of thirteen patients, and there was no increase in body weight other than that attributed to increased appetite and well-being with a subsequent increase in caloric intake.

5. The side effects observed were mild and few consisting of increased appetite in eight patients, mild insomnia in four, epigastric distress in two, and palmar perspiration in one.

6. The therapeutic effectiveness of long term prednisone therapy and the ultimate undesirable effects must be based on further clinical observation and study. Close observation and supervision should be exercised to prevent serious side effects of hypoadrenalism following prolonged use of this drug.

7. The effectiveness of cortisone-like drugs in the symptomatic relief of bronchial asthma should not preclude the intensive and continued search for the causative agents and, when determined, specific hyposensitization should be instituted against these etiologic factors if they cannot be eliminated.

8. Prednisone is a useful drug in the control of the symptoms of chronic bronchial asthma while the search for the offending agents is in progress.

We wish to acknowledge the kind assistance of Mr. Harold Woodson, biochemist, Department of Pathology, Provident Hospital, for making 17-ketosteroid, serum sodium and potassium determinations.

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OBVIATING THE ANTIHISTAMINIC SEDATIVE FACTOR WITH A NEW ANTIALLERGIC

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ABOUT one out of every twenty prescriptions written is for an antihistaminic. Despite this large prescription volume, much of the therapeutic value of antihistamines is nullified by their disconcerting sedative effect.

According to Marsh,[8] there are about 4000 compounds described in the medical and patent literature as possible antihistaminics. However, only about 100 preparations have been tested in man and, of these, twenty are available in this country. In the entire twenty there is no one compound which does not have some sort of sedative effect ranging from mild to moderate to severe. The problem of sedation with the antihistaminics, therefore, is a well recognized one.

In a discussion on side reactions with antihistaminics, the New and Nonofficial Remedies for 1954 states, "The most common untoward reaction is sedation. This varies from mild sedation to deep sleep, depending on the particular drug, the individual response, and the dose. Inability to concentrate, dizziness, and disturbed co-ordination are related to sedative action."[11]

In a recent article Galambos[6] pointed to this factor by stating, "It is evident that all antihistaminics possess side effects, most important of which are sedation, drowsiness, and sleepiness. These side effects interfere with the daily routine of the patients and militate against the usefulness of the drugs. Patients are advised not to drive cars and not to sign checks and papers while under the effects of these drugs."

Cooke,[2] in writing about the value of antihistamines, also mentions this weakness by stating, "They do not satisfactorily replace specific therapy, since side effects such as somnolence limit the amounts that may be required to control symptoms."

There may be a way, however, to improve the effectiveness of antihistamine therapy by circumventing or offsetting this effect. New and Nonofficial Remedies[11] advises a conjoint administration of a cerebral stimulant and an antihistamine, if the problem cannot be solved in any other way (i.e., replacing one antihistamine with another, et cetera).

Recently, attention was called to a single tablet which contains a cerebral stimulant and an effective antihistamine. This preparation, Plimasin®*, contains 25 mg tripelennamine hydrochloride (Pyribenzamine®) and 5 mg methylphenidylacetate (Ritalin®). The combination of a well-known potent antiallergic with a mild analeptic tends to reduce sedation to such an extent that it is practically negligible. Feinberg[4] and others[7,9] found

*Supplied by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

it an effective antihistaminic with an exceedingly minimal sedative effect. Arbesman,[1] reporting on the findings of the Committee on New Drugs of the American Academy of Allergy, pointed out that with Plimasin "the usual sedation seen with antihistaminics is almost absent."

TABLE I.

Per Cent Relief	Allergic Rhinitis	Bronchial Asthma	Urticaria	Dermatitis
None (25%)	0	0	0	0
Fair (25-20%)	4	1	0	0
Good (50-75%)	35	1	2	1
Excellent (75-100%)	41	0	0	0
Total	80	2	2	1

The literature on the effectiveness of tripelennamine hydrochloride as an antihistamine is extensive. Clinical and laboratory trials with methylphenidylacetate have shown it to be extremely effective and safe to use as a cerebral stimulant,[3,5,10] its action lying somewhere between amphetamine and caffeine.

Eighty-five of the author's patients, who had minimal to marked side effects with other antihistamines, were given the new preparation. Eighty of these patients were suffering from allergic rhinitis, two had bronchial asthma, two had urticaria, and one had dermatitis. The average dose given was three tablets per day. The results of the clinical study are given in Table I.

In the eighty-five cases, eighty of which were suffering from allergic rhinitis, only five had fair relief, all the others had good to excellent relief. Four of these eighty-five cases had side effects, and of these only two complained of slight drowsiness. Significantly, these patients complained of the same symptoms with other antihistamines as well. Eighty-one patients had side effects with previous antihistaminic therapy but complained of none with the new product.

In the author's opinion, Plimasin, because of its moderately stimulating action, should prove to be particularly effective as an antihistaminic in those patients who require antiallergic therapy, yet must and should remain alert and awake—drivers of cars, buses, trains, et cetera; construction workers; and all day-time workers.

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PROPHYLACTIC INOCULATION AGAINST HAY FEVER

(Historical Document)

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Hay fever is a form of recurrent catarrh affecting certain individuals during the months of May, June, and July. It is caused by a soluble toxin found in the pollen of grasses. The patients present the idiosyncrasy of being sensitive to this toxin, which is innocuous to normal individuals. The idiosyncrasy may be detected during any season of the year by dropping a little of an extract of grass pollen into the eye of the suspected individual; a reaction, described more fully below, will be obtained in the case of a hay fever patient, but a normal man will show no effect.

Bostock[1] (1819) recognized the seasonal recurrence of hay fever as separating it from other forms of catarrh. Blackley[2] (1873) advanced much evidence in favor of the pollen theory of its causation, but we owe chiefly to Dunbar[3] (1903) the exhaustive scientific proof of this theory. Dunbar showed that not only all the mucous membranes but even the skin of hay fever patients is sensitive to pollen toxin in a way not shown by normal individuals. He also proved that the injection of the pollen toxin gives rise in animals to the production of an antitoxin having a specific power of neutralizing this toxin. Further, in hay fever patients, he showed the occurrence of some of the reactions associated with the production of immunity:—namely, a specific precipitation of pollen extracts by the patient's serum, and the phenomenon of complement deviation, during the hay fever season, and persisting for a short time after this. Pollen toxin is, therefore, a body capable of giving rise to the production of antibodies in animals and even in hay fever patients, subjected to its action. It is also undoubted that hay fever patients sometimes become cured of their idiosyncrasy. The most reasonable explanation of this phenomenon would seem to be, that the cured patients have had the good fortune to develop an active immunity against the toxin, to the action of which they have been liable for so long.

The repeated absorption of toxin at short intervals is, however, more likely to induce a condition of hypersensibility, and this is the more usual fate of the patient, who becomes only more sensitive during each succeeding season. The local application of a specific serum, such as pollantin, offers a reasonable method of treatment, but one which is difficult and laborious, and which is not calculated to bring about a permanent cure. Cures are, indeed, ascribed to the use of this remedy, but admittedly in exceptional cases; and where the conditions are not understood and the experience is not constantly repeated, one must hesitate to attribute the

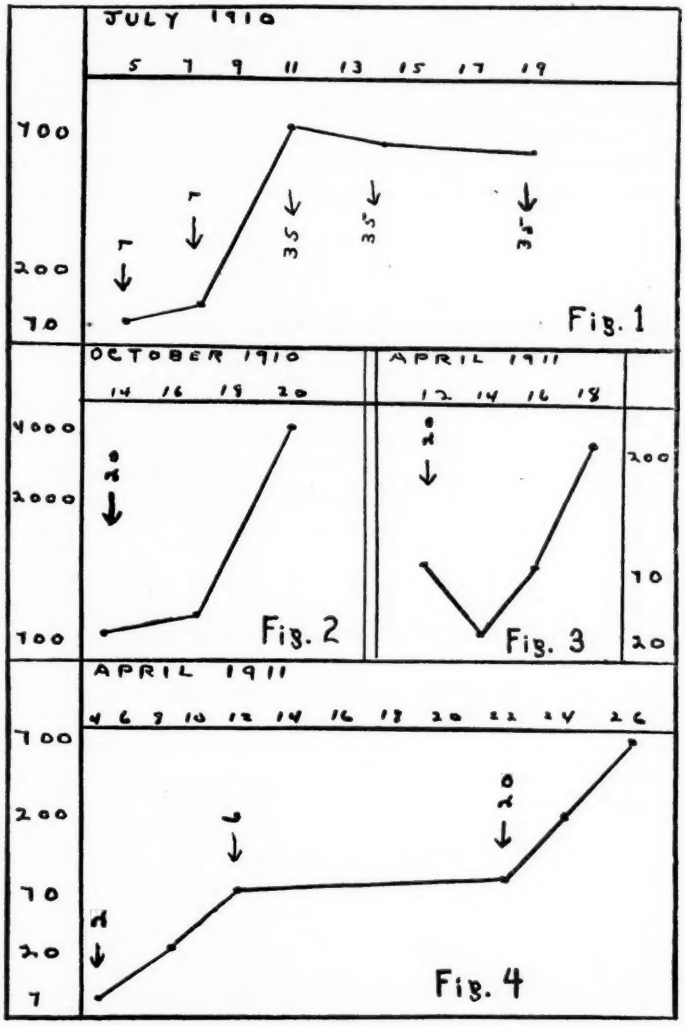
Reprinted from *The Lancet*, June 10, 1911, pages 1572-1573.

result to the cause cited. On general grounds a much more satisfactory result would be expected from the induction of an active immunity, and it seemed worth while to put this expectation to the test of experiment. The questions to be answered are as to what degree of immunity can be induced in hay fever patients by inoculations of pollen toxin, how these inoculations may best be regulated, and whether the affection can by this means be permanently cured.

With this end in view the experiments here described were undertaken in the past autumn, winter, and spring to study the reaction of hay fever patients towards inoculations of pollen toxin. The off season of the year, when the patients were not exposed to spontaneous inoculations, was favorable to this investigation, as the scheme of dosage was then not liable to be upset by spontaneous absorption of toxin from the air, laden with actively poisonous pollen grains. The plan of experiment was to obtain a numerical measure of the sensitiveness of the patients to the pollen toxin and to observe whether this was increased or decreased by subcutaneous inoculations of various quantities of pollen toxin. These observations can be conveniently carried out by the method described below, and it was found that, with well-regulated dosage, it was possible in every case to raise the patient's resistance, to a marked degree, within the lapse of a few months, while, on the other hand, ill-regulated dosage was at once made evident by a decrease in the resisting power.

The pollen extract used was prepared by Dunbar's method of extraction with distilled water, aided by freezing and thawing several times. The extracts were boiled for ten minutes after having been sealed in glass tubes; this treatment was not found to decrease their activity at all. The pollens tested were grass pollens of different species—*Phleum pratense, Poa trivialis, Holcus lanatus,* and *Agropyrum caninum.* These pollens were all found capable of exciting an energetic reaction when instilled into the conjunctival sac of hay fever patients. Timothy grass *(Phleum pratense)* was found to yield the most active extract, and this extract was consequently used throughout the rest of the experiments. One gram of pollen was extracted with 50 cc of water. The activity of this extract may be judged from the fact that one drop of a five thousand-fold dilution is sufficient to excite a distinct reaction in the conjunctiva of the more sensitive patients.

In order to express the strengths of pollen extracts used in testing patients and the doses of pollen toxin given subcutaneously, a unit of pollen toxin has been arbitrarily chosen. This unit is the quantity of pollen toxin which can be extracted from the thousandth part of a milligram of *Phleum* pollen, and it has the advantage that all the quantities used can be expressed in whole numbers. The strength of a pollen extract is given below in terms of the number of such units contained in a cubic centimeter of the extract. Extracts of other pollens have been standardized against the *Phleum* extract by comparative tests on the eyes of hay fever patients.



The numbers at the side denote the resistance of the patient, given in terms of the strength of pollen extract, one drop of which was sufficient to excite a conjunctival reaction. The arrows indicate subcutaneous inoculations of pollen extract, quantities given in the units described in the text. Figures 1 and 2 refer to one patient at different periods of treatment; Figure 3 shows the response obtained after about a month's treatment in another case; and Figure 4 the early stages of treatment.

A measure of the patient's resistance during the experiments is obtained by observing the strength of pollen extract necessary to excite a conjunctival reaction. One drop of the diluted extract is instilled into the eye. The reaction obtained consists in a reddening of the caruncula and, to a lesser degree, of the palpebral conjunctiva, together with a slight injection of the vessels of the ocular conjunctiva and some lacrymation. The patient experiences a feeling of burning and itching. These signs reach a maximum in about five minutes, and a little later there may be a slight attack of sneezing. The reaction lasts as a rule about half an hour. The strength of the extract, which is just sufficient to give this reaction, is used to describe the resistance of the patient. The most sensitive patients examined gave before treatment a distinct reaction with a dilution containing only four units per cc, their resistance is described as 4; the least sensitive reacted to a strength of seventy units per cc, or, in other words, had a resistance of 70. Normal individuals fail to react with the strongest extract (strength 20,000 units) and even resist the application of fresh pollen dust to the conjunctiva. Their resistance is therefore, by our scale, more than 20,000, but it is not infinite as a cubic centimeter of this extract injected beneath the skin of a normal man has been found to give rise to a slight local swelling and tenderness lasting for about twenty-four hours.

Course of Immunization.—Patients received subcutaneous injections of pollen extract. At first very minute doses were given at intervals of three or four days (Fig. 1), and the resistance of the patients rose rapidly; on increasing the dose, however, it was found that the resistance ceased to rise and even went back towards its original value. Longer intervals were then allowed to elapse between successive inoculations. The patient to whom Figure 1 refers had a three months' respite and, after that interval, responded to a moderate dose in the way shown in Figure 2. It is not necessary, however, to leave such a long interval as this between the doses; ten days or a fortnight are, as a rule, sufficient, and at the beginning of treatment, when small doses are being given, a week is enough (Fig. 4). After some time, when the resistance has been considerably raised, small doses cease to have any effect. On increasing the dose it is found that the first effect of the inoculation is to lower the resistance for a few days, giving a *negative phase,* after which the resistance rises again and passes beyond its former maximum (Fig. 3). Ultimately a stage is reached at which the resistance, as measured by the ocular test, ceases to rise, or rises so slowly that the alteration is only obvious after prolonged observation. At this stage the patients will withstand gradually increasing subcutaneous inoculations without showing a negative phase. In the early stages of immunization it is possible, by an overdose, to in-

(Continued on Page 719)

Editorial and Historical Note

A LESSON TO BE LEARNED

It is always wise for those of us who are serious students of allergy to know what evolutionary processes occurred in the development of therapeutic techniques. One of my patients (a man, aged sixty-two, ambulatory, intractable asthma) visited a physician (300 miles distant) licensed to practice medicine, and received the following set of instructions on September 28, 1954:

DIRECTIONS FOR MR. X.

1. For tickling in throat, add two teaspoonfuls of apple cider vinegar to a glass of water and sip as needed to stop the throat tickling. Purchase Heinz cider vinegar as the whole apple is used in preparing it. Any apple cider vinegar whose label states the whole apple is used is all right to purchase.

2. Lugol's solution of iodine will thin the secretion in your breathing tract. At your best meal each day for one week, add two teaspoonfuls of apple cider vinegar to a glass of water in order to make the water acid in reaction. Then add one drop of Lugol's solution of iodine to the same glass. Stir the contents of the glass and take during the meal as you would a cup of tea or a cup of coffee. After one week, take the Lugol's solution of iodine and apple cider vinegar mixture on Tuesdays and Fridays each week in order to maintain the intake of iodine needed by the thyroid gland to sterilize the blood, should harmful germs be circulating in it.

3. When secretion thickened in your breathing tract, shift your daily food intake away from foods that thicken secretion to foods that thin it. Wheat, white sugar, muscle meats such as beef, lamb and pork, orange juice and grapefruit juice all thicken secretion. Corn or rye foods, honey, fish and other seafood, cold country fruits such as grape juice, apple juice and cranberry juice all thin secretion.

4. The result of body-cell activity is the production of heat, energy, carbonic acid, lactic acid, phosphoric acid and sulphuric acid. When you lack energy, and the skin of your forearm and your urine are not acid in reaction when Squibb's Nitrazine Paper is used, your human machine is stalling. You need an increased intake of potassium and the associated acid in order to get your human machine working properly again; when it works correctly, your energy will return and your skin and urine be acid in reaction.

5. Try to remember that potassium is to the nervous system what calcium is to bones. Potassium calms down the nervous system and slows the heart. Study the list of potassium foods given you in order to become familiar with potassium-containing foods. Junior foods in bottles sold at the grocery store represent an easy way of getting the potassium found in fruits.

6. *To produce sleep at night,* make a stock mixture by adding three teaspoonfuls of apple cider vinegar to a cup of honey. Place this in a container that will admit a teaspoon. At bedtime, take one or two teaspoonfuls of this mixture. Honey is in the blood stream twenty minutes after it is taken. If at the end of an hour sleep does not come, take another one or two teaspoonfuls of the apple cider vinegar and honey mixture. Should you wake up during the night and fail to fall asleep readily, take another one or two teaspoonfuls.

7. Should your appetite lessen, it can generally be restored by taking sour drinks.

8. In order to change your body chemistry, place the feet and ankles in a hot foot bath for twenty minutes. You can do this any time of day. Bedtime represents a good time to do this. This hot foot bath is a sedative to the body. The blood in your body makes a complete circuit in twenty-three seconds. Each time the blood goes through your feet in the hot foot bath, it is chemically changed for the better. Remember to use the hot foot bath as a substitute for the sun bath the animals take frequently.

9. Soap is very alkaline in reaction. Try to avoid its use as much as possible, especially should your urine reaction show a blue Nitrazine paper test which means your urine is alkaline.

10. You can control your bowel action by taking honey. Honey has a mild laxative action. If constipation should appear, take a little more honey. If looseness of the bowels should appear, lessen the amount of honey taken. The standard dose of honey is two teaspoonfuls; experiment a little until you find out whether this two teaspoonfuls of honey should be taken once or several times a day in order to keep your bowel action normal.

11. When you have gas formation in your stomach, shift from white sugar to honey. Honey leaves the digestive tract within twenty minutes' time so that does not cause fermentation in the stomach with gas formation.

12. To check your heart use the following:

(A) Pinch each fingernail of one hand. This will make the fingernail white. Note whether the pink color quickly returns to the fingernail when the pinching stops. If it does return quickly, the blood is like water as it should be. If the pink color returns slowly, the blood is too thick and needs to be thinned with an acid and potassium so that it will make its way through the tiny blood vessels quickly.

(B) When you get into bed at night, lie on your left side for a few minutes. Listen to the pulse as you hear it in your left ear. If it is soft, it is all right. If the pulse is loud and hammer-like, it indicates your blood is too thick, and the heart needs to beat stronger in order to force the thickened blood through the tiny blood vessels. You need acid drinks and potassium.

(C) Count or rather take your pulse after exertion such as going up a flight of stairs. If your pulse skips, your blood is too thick with the result that the heart has difficulty in circulating it. You need to thin your blood.

(D) Take your pulse while resting and note whether it skips, indicating a blood that is too thick to be circulated by the heart easily.

(E) Study the character of your pulse in order to know how it is when you are having a good day.

13. Check your skin on the inside of your forearm one or more times a week in order to learn whether your skin when moistened with water from the cold water faucet turns the Nitrazine paper yellow, showing the skin is acid which it normally should be.

14. Study your urine reaction with Squibb's Nitrazine Paper as outlined on the form given you.

15. Every twenty-eight days, we get a new set of red blood cells. We build these with the food we eat and the liquids we drink. Every five months, we grow a new thumbnail. Every ten months, we grow a new nail for the big toe. The normal number of times we pass urine in twenty-four hours is four to seven times.

16. An excellent pick-up drink is represented by the following:

2 teaspoonfuls of apple cider vinegar
2 teaspoonfuls of honey
the above added to a glass of water

Can we learn from our colleague how to treat asthma? I can vouch for the failure of his recommendations to this patient who travelled 300 miles to see him. Or can we learn from his successes with others? Is he treating the body or the mind? There is a lesson to be learned, and it is not too late to face our responsibilities.

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PROPHYLACTIC INOCULATION AGAINST HAY FEVER

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duce a severe attack of hay fever lasting nearly twenty-four hours; this has not been observed in the later stages.

The result of these experiments so far is to show that the sensibility of hay fever patients may be decreased, by properly directed dosage, at least a hundredfold, while excessive or too frequent inoculations only serve to increase the sensibility. It still remains to be seen whether the immunity thus attained is sufficient to carry the patients through a season without suffering from their annual attacks of hay fever. Patients are under observation who have undergone treatment for periods varying from a few weeks to eight months.

It is hoped that these cases will afford material for a further report after the present hay fever season. This work is now in the hands of my colleague, Dr. J. Freeman, who very kindly came to my assistance and carried on the observations during my enforced absence of some months.

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Devonshire-place, W.

Progress in Allergy

DERMATOLOGIC ALLERGY

Critique and Review of the Recent Literature

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The purpose of this review of the literature in dermatologic allergy for 1954 is to correlate the contributions in this field emphasizing the newer developments and make an attempt to supplement the material presented in the Progress in Allergy series by Collins-Williams and Ratner, as well as Halpin in general allergy and Kohn in physical allergy. Hundreds of contributions in the worldwide literature on allergy are available for review and a certain amount of overlapping as well as omission of some material is inevitable. Inclusion of articles is based on interest, fundamental advances, practicability and usefulness to the busy allergist in his everyday experiences with allergic practice.

The format of this review will follow the same outline presented last year by this reviewer and will include contributions in studies of allergic eczematous contact dermatitis, atopic dermatitis, urticaria, drug eruptions, steroid hormones and miscellaneous allergies. Again the reviewer will avail himself of the privilege of comment on some of the work presented.

ALLERGIC ECZEMATOUS CONTACT DERMATITIS

Experimental Studies.—A number of reports in this field involve the use of the corticotropins, and these will be found under this subdivision of this review. New compounds of cortisone and hydrocortisone have appeared. Although considerable literature is accumulating on these compounds, no attempt will be made to assess their value here. Nevertheless, these advances in the fields of corticotropins and steroids represent one of the exciting and dramatic phases of the progress in allergy.

Studies in antibody formation and response continue to appear in the immunologic literature. Antibody response by agglutination tests was studied by Adams[1] in a group of eleven allergic male students suffering from chronic asthma, hay fever or eczema. A control group of normal students was used. Patients were immunized with TAB vaccine. Agglutination tests showed that there was a greater antibody response in the individuals who were allergic, and it is suggested that allergic persons may have an increased capacity to form antibodies. Haxthausen,[76] a well-known student of antibody formation, found that he could transmit specific reagins to the skin with plasma or serum but he could not do this with the injection of lymphocytes. Even though these experiments do not demonstrate formation of any reagin by injected cells, the negative result is considered to suggest that reagins are not formed by lymphocytes, but it is not positive proof in this respect. It is simply another experiment. Walzer and Blazer (1950) had reported that the intracutaneous injection of viable leukocytes obtained from the blood of atopic dermatitis subjects

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who respond with immediate whealing reactions to skin tests with common allergens may specifically and locally sensitize the skin of normal recipients. Haxthausen[75] also studied the effect of a specific antigen in patients with known sensitivity to cobalt. It is known that the skin of animals sensitized with various antigens acquires a specific faculty for retaining or binding the antigen in the skin. Three patients who were known to be allergic to cobalt and who had an intense eczematous reaction to patch tests with 1 per cent cobalt chloride were given 0.1 cc of radioactive cobalt (CO^{60}) diluted with saline solution so that the concentration corresponded to 0.5 per cent cobalt chloride. Radiation from the injected cobalt was measured regularly by a Geiger-Müller apparatus. Controls were used. Haxthausen showed that absorption of injected cobalt proceeds at the same rate in allergic and controlled subjects. This occurs rapidly during the first hours and is practically complete in twenty-four hours. About 90 per cent of the injected cobalt had disappeared before any allergic reaction had become visible. This experiment indicates that in this situation, at least, specific binding and retention of the antigen in the skin do not occur.

Hagerman[73] labeled lymphocytes in guinea pigs using a fluorochrome, acridine orange dye. The lymphocytes so labeled were injected into guinea pigs intravenously or intraperitoneally, and frozen sections were studied microscopically using fluorescence and phase contrast illumination. Labeled lymphocytes were found in the skin one hour after intravenous injection and two hours after intraperitoneal injection. Because of this finding it is difficult to explain why epidermal hypersensitivity cannot be transmitted by direct injection of lymphocytes into the skin as is done in the Prausnitz-Küstner reaction. It is thought that the injected lymphocytes may act as a foreign body in the tissue and are held or fixed in the tissue. It is possible that the eczematous antibodies may be fixed or inactivated in a similar manner.

The intracutaneous injection of crystalline egg albumen bovine gamma globulin in normal and sensitized rabbits was fixed with fluoroscin labeled homologous antibody by Waksman and Bocking.[187] Skin and lymph nodes were then studied under the fluorescent microscope. The amount of antigen present in the tissues was evaluated by the intensity of staining with fluorescent antibody. Antigen was taken up by histiocytic cells in normal rabbits, both at the injected sites and in the sinuses of the adjacent draining lymph nodes. It was felt that considerable quantities remained extracellular and were dealt with elsewhere in the body. Polymorphonuclear leukocytes were actively present in the skin responses but did not contain intact antigen. Many lymphoid cells in the draining node were seen to contain antigen. In animals which were passively sensitized, antigen disappeared more slowly from the skin sites and lymph nodes than in the normal rabbits. Animals sensitized with Freund's adjuvant showed this effect to a greater extent. It was suggested that antigen diffused more slowly into the general circulation in sensitized animals, either because of local edema or by combination with specific antibody.

With our present technique of patch testing, unsatisfactory results are sometimes seen because the patch test slips or contact with the skin is lost because the patient moves about. Actually this produces false negative reactions. Fernström[49] used a special sponge over the patch to provide compression and keep the patch in place. The technique involves the use of blotting paper as patch test material, which absorbs the patch test solution, covered with a 21 by 21 mm square of rubber cloth or cellophane

over which a block of sponge plastic, 19 by 19 by 4 mm, is placed. This is then taped to the skin. Fernström found response to the pressure test was stronger in sixty-two instances, or 51.2 per cent, similar in forty-five, or 37.2 per cent, and weaker in fourteen, or 11.6 per cent. This test is best used with aqueous material, since ointments are actually pressed away from the center of the patches by the pressure and may produce false negative reactions.

Mason and Lada[104] made a conjugate between human serum albumin and a prototype of the poison ivy allergens, 3-N-pentadecylcatechol. This conjugate was injected into the guinea pigs which were subsequently tested for susceptibility to sensitization by 3-N-pentadecylcatechol. Untreated animals and animals given albumin only were used as controls. It was found that parenteral injection of the conjugate conferred some resistance to subsequent contact sensitization. Absolute inhibition of sensitization within twenty-five days after exposure to adequate doses of the antigen occurred in the conjugate-treated group. After this time the results were variable. Incidentally, it was shown by Sulzberger some years ago that parenteral injections of neoarsphenamine had an inhibiting influence on the capacity of guinea pigs to show further allergic sensitization to this agent.

Cormia and Kuykendall,[28] using freshly prepared histamine phosphate in a special buffer diluent, found the end point, called the itch threshold, which is the greatest dilution of histamine that produces recognizable pruritus. These authors reported that an antihistamine, luvistin, and an analgesic drug, tralgon, most effectively controlled pruritus. Niacin, as well as epinephrine, had a favorable effect on itch threshold. Other drugs affecting the itch threshold favorably were acetylsalicylic acid, sodium pentobarbital, caffeine and mephenesin. Cortisone had little measurable effect on the control of itching according to Cormia and Kuykendall. The effect of calcium gluconate and two local antipruritic preparations was negligible. Topical application of chelating agents showed promise. In the original article, which is an excellent piece of work, the limitations of this study are discussed.

Burckhardt showed that persons with alkali dermatitis have less ability to combat alkali, in that it takes them longer to regain normal skin acidity after exposure to basic substances. Cornbleet and Joseph[29] used ion exchange resins as indicators to study the recovery of normal and eczematous skin following exposure to alkali. They found that a patient with eczema shows poor buffering and low base binding capacity of the skin colloids. Normal subjects showed less abrupt changes of the hydrogen ion concentration following exposure to soaps. Pillsbury, in a discussion of this paper, warned about the too ready acceptance of the acid mantle of the skin. He pointed out that bacterial invasion occurs just as readily at low as at high hydrogen ion concentration. As a rule an eczematous skin has been found to lose its acid mantle and show a higher than normal hydrogen ion concentration.

Those interested in the field of connective tissues can find considerable information about collagen in the Transactions of the Fourth Conference.[27] The problem of future study on mucopolysaccharides in the ground substance of the connective tissues is thoroughly aired. Since all sections contain much free discussion, this book should be of particular value to those who are interested in the otherwise unpublished ideas and thoughts of a number of workers in the general field of connective tissue.

Callaway and Hambrick[18] have done an extensive piece of work, sifting 220 references on animal research, which was responsible for the development of a large mass of scientific knowledge in dermatology and allergy. In the field of epidermal sensitization the guinea pig has been used in experiments with poison ivy antigen, dinitrochlorbenzene, aromatic amines, dyes and arsenicals. Rabbits are not easily sensitized to poison ivy. Guinea pigs could not be sensitized to orris root, giant ragweed or sage. Sensitized guinea pigs were treated by various extracts of poison ivy by mouth and by intramuscular injections. The former route seemed to be more efficient in building immunity. Guinea pigs could be desensitized by repeated application daily of a ragweed extract, a process analogous to "hardening" observed industrially in human beings. Guinea pigs previously sensitized to 2:4-dinitrochlorbenzene showed no greater tendency to become sensitized to ragweed than did previously nonsensitized animals.

Attempts to sensitize guinea pigs to nail lacquers and brilliant green failed. In small groups of guinea pigs, severe artificial fever reactions prevented the development of skin hypersensitivity to turpentine. Guinea pigs which were sensitized to phenylenediamine and which received a total body irradiation of 175 r showed attenuation of the degree of skin sensitivity when compared with nonirradiated controls. Guinea pigs were used by Haxthausen that were sensitized to dinitrochlorbenzene and a transfer of sensitivity was effected by the use of a peritoneal exudate injected intraperitoneally into nonsensitized receptor guinea pigs. Passive transfer of the sensitivity was not possible by intradermal injections of the exudate in guinea pigs. Guinea pigs may be made more sensitive to contact by disturbing their normal sleep cycles and by other neurogenic factors. Systemically administered cortisone increased the skin reactions caused by primary irritants, such as croton oil, and the hypersensitivity reactions to 2:4-dinitrochlorbenzene in guinea pigs. Sensitization could not be prevented by systemic administration of cortisone. Callaway and Hambrick also reviewed the function of small animal experiments in the study of the epidermis, hair, pigmentation, tumor production, anaphylaxis in animals, nutrition, metabolism and infections. Sulzberger[177] discussed the limitation of animal experiments when compared to the human, and pointed out that some agents have a dramatically opposite effect in rats as contrasted with mice. Penicillin, for example, is primarily exceedingly toxic for animals and might never have been used in human beings if the experiments were limited to small animal work. Rostenberg,[151] in this connection, also made a few interesting points. Even in the same species of animal there may be profound chemical differences. The Dalmatian dog differs in its uric acid metabolism from all other breeds of dogs. In some work that he had done with ferrets he discovered that he was using a North American ferret which is actually quite different from the European ferret. He stated there are at least three distinct genera among hamsters.

Crissey[32] noted that, among the thousands of compounds which are used in dermatologic therapy, many are useless or even harmful. He outlined a technique for the establishment of standards for comparison of proposed new forms of treatment by fitting frequency curves to histograms of known skin diseases. Data of proposed new forms of treatment would be carefully evaluated along a frequency curve using accepted and supposedly effective agents for the management of skin disorders. This idea was used in fitting normal logarithmic curves to data from 221 cases of pityriasis rosea and 102 cases of alopecia areata. Fifteen patients with

pityriasis rosea were treated with antihistaminics and the data were submitted to a significance test, using the frequency curve fitted to data collected from 221 patients with pityriasis rosea treated symptomatically. It was concluded that antihistaminics did not shorten the course of pityriasis rosea.

Clinical Studies—The ideal prophetic patch test has yet to be perfected. Traub et al[184] discussed the three commonly used methods of prophetic patch testing of dermal products for their irritation and sensitization potential. The first of these is the technique of irritation of the conjunctival sac in rabbits, used routinely in toxicology. In general, the conjunctiva of the rabbit is far less sensitive than is the skin. The second method, which is also an animal test, is the repeated intradermal insult test in guinea pigs, devised by Landsteiner and Jacobs (known also as the Draize test of the Pharmacology Division of the Food and Drug Administration). In this test the animal receives an intradermal injection of the test substance in appropriate dilution every other day for ten injections or a period of twenty-one days. Then three weeks later a challenge injection is given at the same site. The response is measured in terms of erythema, induration and vesiculation as one would in testing human subjects. It must be remembered that the animal skin lacks sweat glands and has a much greater number of hairs, hair follicles and sebaceous glands. There are many inconsistencies in this type of testing especially when patch tests are used and it is for this reason that intradermal injection is the method of choice. The third method, that of Schwartz and Peck, is the prophetic patch test on human subjects. A closed patch test is applied for forty-eight hours. Two weeks later the patches are repeated at approximately the same sites and again readings of dermal response are made. As a corollary to this test Schwartz and Peck also recommended comparative use tests as the final means of evaluating products which had satisfactorily passed the patch tests (Cosmetics and Dermatitis, New York, Paul B. Hoeber, Inc., 1946). Traub and his co-workers tested a number of substances by devising a test which mimics as closely as practical the actual use of the product. By combining a product-use test with the Schwartz-Peck prophetic patch series in the same subjects, the authors designed an irritation-sensitization testing technique that not only predicts the likely incidence of dermal reactions from the use of the product, but also supplies repeated, prolonged contact exposure comparable in frequency with that of the guinea pig intradermal test. In discussion of this paper, Rostenberg[152] pointed out that, percentage-wise, if a group of 200 individuals is tested and zero reactors result, all that can be said is that in the universe at large there are fewer than 5 chances in 100 that more than 1.5 per cent will react to that material under the conditions of the test employed. Hence, not more than fifteen persons in every 1,000 will develop a reaction under those conditions. If 0.1 per cent of all persons react to a given compound, that is 1 to 1,000, and subjects are taken at random off the streets in groups of 200, a reactor will not be found in every random group of 200 because the incidence is only 1 to 1,000. In further discussion, Sulzberger[178] mentioned some examples that indicate the difficulty of the problem of a prophetic patch test. He stated that animal work would not have indicated that certain shampoos actually produced blindness when they got into the eyes. Skin tests would not have foretold this complication. Another difficulty that probably could not be foretold was the problem

of nail lacquers used as undercoats. This posed a problem because of the severe reaction occurring in human subjects owing to the length of time and penetration of these preparations. He also mentioned certain antifungal agents that were used on the scalps of children which produced convulsive seizures and deaths in a few of these children. He does not believe that this could have been foretold by any system of testing. The limitations of our standard prophetic patch testing procedures are obvious.

Noojin[117] traced the development of the growth of industrial dermatology and the clinicians who have made outstanding contributions to this field. The subjects of dermatophytosis in industry, the patch test, "hardening" in industrial allergic dermatitis, and classifications of irritants are briefly discussed. He noted that, during and since World War II, industry in the United States has continued to be plagued by many varieties of industrial dermatoses, estimated to cost more than $100,000,000 annually. The majority of these have been attributable to contact with: cutting oils, solvents, greases, rubberized compounds, strong soaps, alkalis, cements, acids, trauma and accidental injury, physical and biologic agents. Although allergy plays a prominent role in industrial dermatoses and accounts for some of the most difficult problems, nevertheless, primary irritants are responsible for 80 per cent of contact occupation dermatoses and sensitizers for only 20 per cent. Farner[48] re-emphasized the well-known fact that 65 per cent of all cases of occupational diseases reported throughout the United States are dermatoses. Causal relationship between allergens and dermatitis is often difficult to establish. Psoriasis or lichen planus about to erupt may frequently make its appearance in a scratch, abrasion or an area subject to friction. If the friction or scratch is acquired on the job, the question may arise as to the causal relation between the lesion and work. Many states have set up vocational rehabilitation services for persons of working age with a fixed or slowly progressive physical, mental or emotional handicap. If a physician refers such a patient to vocational rehabilitation while still caring for him, assistance will be given in getting the patient back to work, so that emotional disturbances, "compensationitis," "welfaritis" and other forms of dependency can be prevented.

Nielsen and Bang[116] repeated standardized patch tests on 103 eczematous patients who had previously shown positive reactions in 1934 or 1935. The authors showed that there was loss of hypersensitivity with resultant negative reactions in about 60 per cent of patients. Some substances showed a negative patch test sooner than others. For example, pyrogallol, anthrarobin-chrysarobin, para-aminophenol and brown soap showed a high percentage of negative results on retesting. Eighteen per cent of patients previously sensitive to nickel sulfate had negative results. Plant oils such as primulin, however, mercury and balsam of Peru were examples of agents which persisted in sensitivity on patch retesting. A short but pithy résumé of the role of the patch test in contact dermatitis is presented by the Council of Industrial Health.[31] The Council is made up of the leading industrial dermatologists in the country. The type of patch test, the site of application and the interpretation of patch test reactions are described. This is a practical discussion which eliminates controversial issues and assumes that the reader has a knowledge of the scientific basis for the application of the patch test. It is to be remembered that a patch test is continually subject to change and that absolute reliance upon its results in all cases of contact dermatitis is not justifiable. An editorial[42] on patch testing further emphasizes to the practicing physician the im-

portance of this useful but specialized form of testing in patients with contact dermatitis.

Rostenberg[150] reviewed the role of allergy in the production of occupational dermatoses. The role played by genetic influences suggests that a patient with a hereditary background of asthma or hay fever is not more likely to develop occupational dermatosis when exposed to strong eczematous allergens. The salient features of the immediate and delayed types of sensitization are discussed. Quoting Gell (Gell, Harrington and Rivers, Brit. J. Exper. Path., 27:267, 1946), it is noted that many chemical compounds which act as sensitizers are capable of forming conjugates; or may be metabolized in the body to a compound capable of forming conjugates; or have the capability of forming strong adsorption complexes with protein. Typical powerful skin sensitizers are acid halides, some acid anhydrides and benzene compounds such as tetryl. Another class are the arsenoxides which combine with the SH groups of proteins. Less active sensitizers are exemplified by p-phenylenediamine and polyhydric phenols (active principle of poison ivy) which are probably oxidized to quinones which in turn react with proteins. Although the epidermis is the shock tissue, the reactions which take place need not necessarily arise because of immunologic processes. The concept of an adaptation of an enzyme system is discussed in the production of an allergic sensitization. "Desensitizing" injections do not desensitize but make a patient more tolerant to the excitant. A worker may lose his "hardening" in industry when removed from the offending material.

Government workers with occupational dermatitis were studied by Becker[7] from July, 1951, to July, 1952. Two hundred and sixty patients were seen in one year in an outpatient clinic in Washington, D. C. The highest number of sensitivities were to chromates found in inks, and in the photographing and printing fields. Nonchromate inks sensitized ten patients; chromate inks sensitized twenty-four patients; rubber nine patients. A higher percentage of allergic sensitization and much less dermatitis from primary irritants than in the usual occupational series were found. Chromate dermatitis was very difficult to manage. Treatment and protective measures were poor and slow. The best attack was improvement in machinery and techniques to minimize the amount of contact to the worker. Calnan[19] described a new "contact clinic" organized at St. John's Hospital in London. The value of patch testing and the pitfalls of interpretation of reactions are related. Patients allergic to nickel, rubber, metals, paraphenylenediamine, and sulfonamides have been retested over many years and still found to be sensitive. A research program was discussed.

Dermatitis in locomotive engineers is usually due to chromates, according to a notation in the *Journal of the American Medical Association*.[139] Diesel motors require water cooling and to prevent corrosion, sodium chromate is in wide use along with certain other chemicals, all more or less harmful. It is introduced into the cooling system in about a 6 per cent solution. Within the radiator, dilution leads to a concentration of 0.08 per cent. If there are leaks in the cooling system the entire locomotive may become contaminated. Leakage of solution is followed by concentration and drying to a powder so that a little chromate may be blown about anywhere on or within the locomotive. A few workmen become "hardened." Barrier creams promise little in prevention. Dimercaprol (BAL ointment), 3 per cent, holds some promise in treatment, but intramuscular

injection of the chemical is useless. Some patients are intolerant to dimercaprol. A 5 per cent solution of sodium thiosulfate used locally has been advocated. Some patients respond to hydrocortisone ointment if exposure no longer exists. Some railroads are resorting to aluminum anticorrosives which, while less effective, are little damaging. A number of high awards ($42,000 in one instance) within the courts under the Federal Employers Liability Act probably will accelerate the shift away from the use of chromate. It is again pointed out that one of the agents in cement which can cause allergic sensitization is chromium. A patient with a strong specific hypersensitivity to potassium dichromate was patch tested by Denton et al[36] on three occasions with 0.005 per cent potassium dichromate solution, and showed the same reaction to this substance that he did to filtrates from washings of Portland cement containing hexavalent chromium in terms of potassium dichromate in concentrations of 0.0001 and 0.0004 per cent. Cement workers, however, may be exposed to higher hexavalent chromium levels than is indicated by analysis of cement washings. As moisture evaporates from cement mixtures in contact with the skin the percentage of hexavalent chromium rises.

Two patients are presented by Booth,[12] both women, aged forty-four and fifty-two respectively, who suffered a subacute eczematous dermatitis on the dorsum of the fingers, hands, forearms, face and neck. Both patients were payroll clerks and prepared pay checks. Postive patch tests with the checks were obtained in both and the wearing of cotton gloves prevented recurrences. The dermatitis apparently comes from special coatings applied to the bank checks to prevent alterations and forgery. A special feature of the checks producing the dermatitis was the appearance of the word "void" in red, after the application of ink eradicator. A number of chemicals were contained in the ink coating on safety-type bank checks. Many of them are known sensitizers. These are the first two cases so reported.

Lanolin hypersensitivity is a rare occurrence. Sulzberger has shown that the causal agent was in the alcoholic fraction. Careful separation of the components of lanolin is a lengthy time-consuming procedure. Everall and Truter[47] found one patient with known sensitivity to lanolin who reacted to a residue characterized as a yellow-glassy solid. Acetylation of this substance prevented its allergenic reactivity by patch test. Lazar[92] reported a case of a twenty-two-year-old white sergeant who was referred to the dermatology clinic at Osaka Army Hospital with a diagnosis of dermatophytosis. On examination, the patient had a vesiculobullous eruption on an erythematous base on the soles and a V-shaped dermatitis on the dorsum of the feet. Further questioning revealed that the patient wore blue rubber zoris as a house slipper and in the shower. Subsequently, patch tests done by conventional methods elicited a vesiculobullous response to the rubber material used in the construction of the zoris. No fungi were found. It was of interest to note an id-like reaction on the hands secondary to a foot eruption which was not mycotic in origin. This tends to support the theory of the occurrence of distant dermatoses thought to be due to local absorption followed by hematogenous spread. Shatin and Reisch[164] attempted to find a basic sensitizing agent in patients presenting shoe dermatitis. The authors studied the shoe manufacturing process in great detail and believed that most patients with shoe dermatitis are allergic to thermoplastic material and various rubbers. Antioxidants and accelerators are the actual sensitizers in rubber. In the construction of a shoe,

thermoplastic material is run over a hot roller before being inserted into a shoe and is then molded into proper shape in the shoe while it is still warm. The two most important types of box toes in men's shoes are made either of thermoplastic material or of flannel impregnated with pyroxylin. The flannel box toe is found only in the higher priced shoes. It is important to note that rubber cements are found in various parts of the shoe and rubber is always present in the midsole. The presence of sensitizing agents in shoes usually accounts for the distribution of the dermatitis as seen in the patient's feet. The reviewer notes that it is practically impossible to purchase shoes on the open market which do not contain rubber in some form. Fortunately, patients with shoe dermatitis are not frequently seen.

Siegel[171] reported a white man, aged forty-four, who complained of burning, itching and blistering eruption in all the finger webs. For two days prior to the occurrence of the eruption he had been "picking black walnuts." This was his first experience. He wore no protective gloves and was not careful about washing his hands. After the eruption subsided, he was asked to shell approximately 4.5 kg of black walnuts and had no recurrence of the eruption. It was felt that the original eruption was caused as a primary irritant effect of the walnut juice rather than an allergic sensitivity. Fisher[52] described contact sensitization dermatitis in the mouth which is caused by dental plates. Ninety per cent of dental plates are processed with acrylic resins. Modern acrylic dentures are self-cured without heat by inducing polymerization of a mixture of methyl methacrylate monomer, and polymethyl methacrylate powder with an organic peroxide and an accelerator or promoter. Since polymerization by this method is not associated with high temperatures, a higher residual monomer content may lead to allergic sensitization. Of twenty patients with sore mouth due to dentures, none was allergic to the completely polymerized acrylic denture. It is of interest that clearing of the stomatitis when a denture is not worn and recurrence of a sore mouth on use of the plate is not proof of allergic sensitization to the denture, according to Fisher. Pressure and trauma of an ill-fitting plate may cause the same symptom complex and this must be ruled out. It is of further interest that when seventy controls had dentures strapped on their forearms for forty-eight hours, all reacted with some degree of redness and papulation. It is concluded that these reactions represent nonspecific pressure phenomena since histologic examination of the bullae reveals simple subepidermal bullae without eczematous response. It is better, therefore, not to test with completely polymerized denture material. Testing with the monomer alone will indicate the presence of allergic sensitization to dentures. A forty-one-year-old dental technician is described by Shellow,[168] who was sensitive not only to the liquid monomer of methyl methacrylate but also to the polymer and the heat-cured denture material as well. This patient had an erythematous, vesicular, scaling-crusted, painfully fissured dermatitis of his fingers for several months. Patch tests were positive to the monomer, the polymer powder and also a small, smooth piece of finished, heat-cured denture. Erythema was evident eight days later and persisted for an additional seven days. It is agreed, however, that sensitization to acrylic denture material is rare.

Adhesive tape causes skin irritations based on three principal mechanism:[136] (1) primary irritation; (2) occlusion, lacerations and infections; and (3) allergic sensitization. The first two are considered to be the

common mechanisms; the third, which results in the more severe forms of dermatitis, is a rare occurrence affecting only a very small number of those exposed. The most commonly responsible chemicals are those of the natural latex rubber mass that forms a principal ingredient of the sticky material in most tapes. The natural pitches and resins, such as Burgundy pitch, and turpines in addition to the man-made adjuvants, such as monobenzoyl ester of hydroquinone or hexamethylenetetramine (urotropin), are often responsible. Certain brands of adhesive tape prove less irritating than others. The addition of certain adjuvants of antibiotics and antifungal agents may be of some use in reducing infection and irritation to adhesive tape.

A salt of thioglycolic acid is used as the essential ingredient for cold permanent waves. Waving of the hair is made possible by chemical changes brought about by the thioglycolate solution. The hair is rendered more plastic and flexible and during this relaxed state, tension is applied in whatever direction is desired. Wavy hair results by winding the hair around curlers. To make the wave "permanent" the thioglycolate solution is neutralized with a bromate or perborate neutralizer, or a slow neutralization by oxidation is utilized. There is no evidence of systemic absorption but allergic sensitization does exist, especially in beauticians. According to a notation in the *Journal of the American Medical Association*,[131] the following precautions should be observed when cold waving permanents are given children: (1) Keep waving lotion away from the eyes, ears, nose and mouth and from the skin as much as possible. (2) Keep waving lotion and neutralizing solution out of reach during the process and discard them immediately after use. Accidental ingestion of these solutions may cause serious results. (3) Do not give a cold wave if there are abrasions or scratches on the scalp. Cold waving solutions for adults preferably should not be used for children. Manufacturers are careful to modify the solutions for children who have finer hair which is less resilient than that of an adult. Children's hair apparently is difficult to curl.

Loewenthal[95] has published a small book on the eczemas, with contributions by internationally known authors on the subject. The book has been very well received. The text and illustrations are excellent. Brunner[15] believes that so-called housewives' eczema is caused basically by an external irritant. He incriminates synthetic detergents, ammonia water, bleaches, phosphates, abrasive powders and organic solvents in waxes and polishes. Emotional upsets may be contributory. He advised avoidance of these irritants, and notes that similar eruptions may occur in bartenders, soda jerkers and others in occupations involving "wet work." The reviewer notes that there have been few carefully controlled studies on the effect of different modern detergents on the human skin, specially of housewives. It is not known whether these are any more irritating than the old household soaps, or how one detergent varies from another. Lyon[100] studied the sensitizing powers of an alkaline-built synthetic detergent of pH 9.8 and a 100 per cent sodium base soap of pH 10.1, both of which are in general use. It is known that in hand laundry washing, the ordinary housewife uses detergents of about 0.3 per cent, but the concentration in the lather usually runs about 8 per cent, varying from 5 to 20 per cent. This probably explains dermatitis of the interdigital clefts and under rings, if the hands are not properly rinsed but merely dried. It seems probable that, among several other factors, the alteration of the molecular structure of keratin is an important but not the only mechanism involved in the

production of dermatitis by detergents. Lyon concluded that alkaline detergents and soaps are poor sensitizers but act as mild primary irritants. Patch tests with these substances show a wide range of variability even when repeated on the same volunteers within a short space of time. Gross et al[70] suggested that housewives' eczema is really nummular eczema and that the chemical action of soap and alkalis is the precipitating factor. This opinion was the result of studies using alkali neutralization tests on patients with nummular eczema, housewives' eczema and other types of eczema and noneczematous skin lesions. They found that there is impaired neutralization of alkali both in patients with nummular eczema and with housewives' eczema. They recommended the use of vitamin A because of its role in the keratinization process of the skin. The usual dermatologic and systemic supportive measures should not be overlooked.

Fredricks and Becker[54] studied 145 patients with vesicular eruptions of the hands and feet in which fungous disease was excluded by previous studies. In 81 per cent of patients, anxiety, tension and nervous fatigue were considered to be major precipitating factors. Associated functional disorders, such as migraine, colitis, anxiety states and behavior problems, were found in 27 per cent of these patients. Thirty-two per cent had concomitant dermatoses such as seborrheic dermatitis, nummular eczema, atopic eczema, anogenital pruritus, urticaria and alopecia areata. Marked hyperhidrosis of the palms or soles, or both, was present in 43 per cent. The authors suggested that in addition to the use of wet dressings and other local measures, the patients be given anticholinergic drugs. In this series, methantheline bromide was prescribed to the point of producing dryness in the mouth. Excellent results were produced in 48 per cent in three weeks time and another 45 per cent were improved in an additional two to three weeks.

Gaul[62] patch-tested 100 patients with various dermatoses and found that thirty-two were sensitive to a metal. Positive reactions were seen much more frequently with metal salts than with the metals themselves. It is of interest that of forty patients with hand eczema, eighteen had positive reactions to metals and, of these, twelve were sensitive to chrome. A 1 per cent solution of potassium chromate may produce a bullous response in some of these patients so that Gaul recommended beginning with 0.1 per cent or 0.05 per cent solution for routine testing. He also found a patient with a positive reaction to gold. She had dermatitis on a finger under a gold ring and showed a papular response to a patch test with a 1 per cent solution of gold sodium thiosulfate. Another patient had a scaly dermatitis of the finger tips presumably from handling coins. The reaction to 1 per cent silver nitrate on patch test was vesicular. Postive patch tests to gold and silver usually are rare.

Sheard[165] reported three patients who were using zinchlorundesal ointment ("ointment new salundek") which contains 5-chlorosalicylanilide. In each case the adult in charge of rubbing the ointment into the scalp of the affected child developed a pruritic maculopapular erythematous contact dermatitis of the hands and forearms. It is of interest that none of the children showed any irritation of the scalp. The contact dermatitis produced in these cases followed the distribution similar to that of typical housewives' contact dermatitis of the hands and, since the scalps of the children did not show irritation, the actual cause of the hand dermatitis could have been overlooked.

Wolff and Sidell[193] presented a patient who was tattooed in June, 1953,

with blue and red pigment on the volar surface of the right forearm. After healing, the red portion of the tattoo continued to be thickened. The patient was aware that he was sensitive to mercury but he did not know that cinnabar, the red portion of the tatto, contained mercury. In discussion it developed that the microscopic picture in a similar situation was difficult to distinguish from lichen planus or lupus erythematosus. It was also felt that this patient should never be given an intravenous injection of mercurial for fear of immediate anaphylactic shock. Epidermal sensitivity in many cases carries with it the principle of generalized sensitization for the individual. Saunders[157] presented the history of a ten-year-old boy who suffered from redness and edema of the upper eyelid and mandibular adenopathy following the local application of a a 1 to 1,000 aqueous solution of Zephiran® chloride. Patch tests to this strength of antigen gave positive reactions. Because this agent is being widely used, it is important to remember that occasional cases of hypersensitivity may occur. George[64] reported a thirty-two-year-old white man with the chief complaints of reddening. itching and swelling of the scrotum and penis. The area of dermatitis also included the lower flanks and both hands. The history indicated that the patient's wife was using nitrofurazone vaginal suppositories following a pelvic operation. A patch test made on the patient's left upper arm with the suppository produced a vesicular and erythematous reaction. It is of interest that the patient required eight weeks of treatment before the erythema and pruritus subsided.

Ayres and Ayres[5] reported the finding of four cases of contact sensitization to chlorcyclizine hydrochloride ointment as proved by patch tests. These were the only cases seen in an extensive use of the preparation over a period of about three years in many hundreds of cases. The authors felt that the agent still has a low sensitization index. Maxson[106] reported a seventeen-day-old infant who was brought to the hospital because of rash and vomiting. The mother reported that four days before admission the baby began to have loose stools and his buttocks became chafed. For two days she powdered his perianal region with boric acid powder and on the third day she substituted boric acid solution for the powder. On the day of admission the skin of the entire body showed a diffuse erythroderma with bullae. In spite of supportive therapy the patient's course deteriorated steadily and he died on the third hospital day. At autopsy, boric acid was demonstrated in the liver tissue. Although the drug is not absorbed from the intact skin it is readily absorbed from any area of broken or denuded skin. The commonest symptoms of poisoning in infants are vomiting. diarrhea, convulsions, coma and an erythematous eruption. The reviewer notes that there are several reports of fatal poisoning from the application of boric acid powder, ointment or solution to the skin. In reviewing a number of these reports, however, there is no clear-cut evidence to indicate that the normal judicious use of boric acid compresses or ointment to limited areas of the skin is harmful. In England there is a move to eliminate boric acid preparations from hospitals.

Howell, Goth and Fashena[81] found that concentrated poison ivy extract is non-nephrotoxic for rabbits. They also reviewed the literature in which claims were made that the administration of Rhus extracts had caused systemic injury and found that the evidence for this was inadequate. None of Shelmire's original patients sensitive to poison ivy showed symptoms of renal irritation. This work was done many years ago. In twenty-five patients with severe, widespread ivy dermatitis, urinalysis during the healing phase was normal in all patients. Patients highly allergic to ivy

who have been given large doses of ivy extract orally have not showed any evidence of kidney or collagen damage. The authors stated that it is possible that secondary infection of the dermatitis resulted in the occurrence of kidney disease, rather than the production of these changes by the antigen. Brachman and Roy[13] reported nineteen patients with pollen and plant dermatoses treated with oral oleoresins by the accepted ingestion technique. Fourteen patients were followed for one to two seasons. On patch test nine were oil-sensitive and five were protein-sensitive. Many were pollen-sensitive on skin test to the oily fraction. Of the nine who were sensitive to oleoresin patch tests, six were improved with treatment. Their experience would indicate that pollen- and plant-sensitive individuals may be protected from minimal and moderate exposures during the season by either oral ingestion or injection of the oily fraction of the plant oil. Patients who have a dermatitis during the ragweed season and who are sensitized to aqueous protein extracts respond at times to desensitization with these extracts, but in no way is this treatment as effective as the oily fraction (Fromer, J. L., and Burrage, W. S.: Ragweed oil dermatitis. J. Allergy, 24: 425, 1953).

The fruit of the Mangifera indica (mango) tree not infrequently produces a severe dermatitis in hypersensitive individuals. Case reports and a review of the subject are presented by Goldberg.[66] The tree is a member of the Anacardiaceae family which includes such well-known plants and trees as poison ivy, sumac, cashew and pistachio. The commonest site for the dermatitis is around the mouth and the hands. The offending antigen is contained in the peel of the mango which yields a yellowish wax-like oil containing cardol which is similar to the sensitizing principle, urushiol, of poison ivy. There may be a seasonal incidence of May, June or July, which is the mango season. Persons who are sensitive to poison ivy have a greater susceptibility to this type of sensitization. Such persons can eat the pulp but should not handle the unpeeled mango. Kaufman[85] stated that dermatitis due to ingestion of alfalfa seed apparently has never been reported, and described two patients, both over sixty, who developed a pruritic eruption beginning on the dorsa of the hands which eventually spread to the arm, eyelids and face. The patients had been drinking an infusion made by boiling two tablespoons of alfalfa seed in a pint of water for the treatment of hypertrophic arthritis. In one instance the patient, after a period of forty days, had a recurrence of the dermatitis ten hours after drinking a cup of alfalfa seed tea. Patients apparently are reluctant to admit taking alfalfa seed and a sharply focused history is necessary to disclose the fact. In the case of any nondescript eruption, particularly in a patient with arthritis or diabetes, the possibility of alfalfa seed as a causal factor should be considered. The dermatitis may masquerade as a "neurodermatitis." Lemmon[30] reported a patient who had a dermatitis several weeks after drinking a quart of alfalfa seed tea daily for chronic hypertrophic arthritis of the spine. It began between his fingers and on the dorsa of his hands and spread to the cubital and axillary regions. When he stopped drinking the tea, the dermatitis promptly cleared.

Suskind[181] made a study of protective or occlusive industrial agents. A cream containing 52.5 per cent silicone fluid incorporated into a bentonite base was used as a protective preparation by 114 workers in one manufacturing plant for eight months and by ninety-two workers in another factory for two months. The skin was freshly cleansed and then the cream was applied to dry skin twice daily. A detergent cake of sodium

lauryl sulfoacetate was used to remove the cream. A fair degree of protection was obtained against irritating corrosion inhibitor dissolved in light mineral oil; degreasing solvents such as xylene and heavy naphtha when used intermittently; lubricating oils and insoluble and soluble cutting oils. If degreasing solvents were used continuously or frequentlv. little protective effect was noted. A good degree of protection was also noted against aqueous solutions of sulfuric acid and against metallic dust. *In vitro* studies showed this silicone cream to be fairly stable when immersed in aqueous solutions of soap, ethyl alcohol, slaked lime and ammonium hydroxide. Sulfuric acid, formalin, cutting oils, light petroleum oils, water and ethylene glycol, also fail to affect the cream when studied *in vitro*. Finnerty[51] studied 109 patients with patch-test-proved contact dermatitis. After the eruption subsided he used a protective cream containing 52 per cent silicone in bentonite (Pro-derna®). The author reported protection for workers exposed to emulsified cutting oils, alkalis, acids, soaps, and many water-soluble irritants as well as heavy oils and greases. The cream is not effective against solvents and fuels. A measure of the protection of this cream may be determined by immersing a glass slide with the protective film applied into the irritant. Stability of the film for three to six hours justifies its use clinically.

A more critical report on this subject is made by Morris.[112] A number of patients were used in this study who had previously been treated for occupational skin eruptions. These patients had showed positive closed patch test reactions to a number of chemicals. They were then advised to apply a silicone protective cream for seven to ten days to the right arm. The creams contained 20 to 50 per cent active silicone ingredient. One cream had a greasy base and the other a greaseless vehicle. At the termination of the application period each worker was retested to the active sensitizer to which he had previously shown a positive reaction. Patch tests were applied to the silicone treated right arm and also, as a control, to the left arm which had previously had no protective cream. Morris recorded six patch test reactions which were more positive on the silicone protected arm than on the unprotected control. No difference was noted in five cases, and 2 patients gave negative reactions on both arms on retesting. Three patients had a complete recurrence of their dermatitis after using the cream and returning to their work. The author thought from this study that these creams offer little protection to the industrial worker.

The frequency of occurrence of otitis externa depends upon the part of the country in which the condition is seen. Otolaryngologists from the South and Southwest report that otitis externa constitutes as much as 40 per cent of their office practice. Otitis externa caused the withdrawal of major numbers of fighting men from active duty in World War II. McLaurin[108] investigated 157 cases of otitis externa and found Micrococci (staphylococci) present in sixty-seven cases. There was only one fungous infection by *Candida* in the entire group. McLaurin cleanses the ear canal, removing the obstructing debris, which provides an excellent culture material. Wicks of Burow's solution are used if irrigations cannot be tolerated, and the suction tip aids materially in the cleansing process. Sensitivity studies are performed after cultures are taken. Sulfamylon® was used in twenty-five of the 157 cases. Neomycin, chlortetracycline and sulfanilamide are all useful topically when they are indicated. Neomycin is particularly effective in *Pseudomonas* infections, which tend to be extremely obstinate. Adjunct therapy which was used

in twenty-seven cases included antihistaminic drugs, staphylococcus toxoid, thyroid extract and calcium. The author is inclined to the opinion that most external otitis is probably a dermatitis on a bacterial basis.

ATOPIC DERMATITIS

Kesten[87] reviewed the records of about 2,000 patients seen over a period of twenty-five years. About two-thirds of the patients in this study were under the age of six, with the onset of eczema usually before six months of age. Disappearance of eczema was noted in two-thirds of 400 patients under the age of three when elimination diets were strictly enforced. The eczema recurred in this group when the specific excitants were again given to the patient. As the patient grew into adolescence and adult life, it became more difficult to assess the importance of sensitivity to foods. Kesten found that young children became sensitized to such common foods as egg, milk, wheat, orange, tomato, cod and potato. It is of interest that it was unusual to obtain a strongly positive reaction to a food that could be eaten with impunity. In addition to dietary control, inhalant allergies were investigated, and about 25 per cent of this series suffered from other major allergies. Some patients were helped by the removal of foci of infection, the use of antibotics and immunization with toxoids or filtrates of bacterial agents. Ten per cent of 200 adults reacted to filtrates and extracts of eighteen common saprophytic fungi. About 5 per cent of the adult patients with eczema showed a local vesicular eruption to a variety of patch test agents. These substances did not seem to cause the eczema but rather contributed to a recurrence or produced a frank dermatitis venenata. Intensive psychotherapy for some of the mothers of forty children may have been responsible for the remission of severe eczema as the child-parent relationships improved. This is a thorough and realistic review of a very difficult problem in allergic and dermatologic management.

Osborne and Murray[121] analyzed the records of 2,500 patients with atopic dermatitis. Seventy-five per cent of patients undergo summer remissions and have a winter recurrence. Other than this factor, patients followed the regular course known to many students of this problem. The opinion is expressed that wool is the dominant allergen in atopic dermatitis, and other factors may be specific hypersensitivity to fungi, Lycopodium, bacterial sensitization, food sensitization and contributory psychogenic disturbances. Because of the dominant factor of wool, Osborne and Murray insist that the patients must live in homes without woolen rugs, carpets, blankets and clothing. The skin of most patients with summer remissions and winter recurrences begins to itch and burn when the amount of wool fiber and house dust exceeds 2 per cent. The average house or apartment which they examined showed a minimum of from 5 to 10 per cent and as high as 50 per cent of wool fiber in house dust during the seven cold months. It is also the opinion of these authors that the vasoconstriction and white dermatographism often seen in patients with atopic dermatitis is a manifestation of wool sensitivity. It is to be remembered that if wool is an allergen capable of causing a reaction on external contact, it may often cause sensitization reactions if the allergen is taken by inhalation.

Thirty-two children with atopic disease were studied by Fries and Borne[57] for the effect of fever and intercurrent infections on the course of their allergeic symptoms. Some of these children had atopic dermatitis.

In one group, the development of Kaposi's varicelliform eruption caused marked temporary clearing of the eczema. A relapse of the dermatitis, however, occurred after the infection subsided. It was noted that fever seemed to be the factor most responsible for the remissions. Measles consistently produced a temporary response. It is thought that cutaneous inflammation, other than an allergic response, may produce or induce refractoriness in the skin and this may account for the improvement noted. Another mechanism introduced was that of the steroid hormones producing an ACTH-like effect in a patient in stress which was not of the prolonged variety. It was noted that infections accompanied by only silght fever may have an adverse effect on the allergic state. The reviewer notes that soldiers who had atopic dermatitis and recurrent malaria did not have a remission of the atopic disease.

The annual summary by Collins-Williams and Ratner[24] of pediatric allergy points up a number of interesting "allergic gems" to be remembered. In a study of 750 cases of allergy in children it was found that 59 per cent had suffered from allergic eczema at one time before the onset of respiratory allergy. Ratner, Collins-Williams and Untracht call this the "allergic dermal-respiratory syndrome." This confirms reports in the literature on thirteen other series of children. In the management of children and infants with eczema, the substitution of goat's milk or cow's milk could be expected to benefit the eczematous state only if the patients were sensitive to the lactalbumin of cow's milk. The lactalbumin of goat's milk is different from that of cow's milk, but the casein fractions of both milks are the same. As a practical point, most children who were allergic to milk could tolerate evaporated or heated evaporated milk without difficulty, since it is felt that the sensitivities when due to the albumin fraction may be tolerated. The albumin is denatured by the process of heat. Ragweed pollen may be an important inhalant factor in the etiology of atopic dermatitis. In such a sensitive patient, repeated inhalations of ragweed pollen can produce a dermatitis. Furthermore, dermatitis may be induced by the injection of ragweed pollen extract given for purposes of desensitization in such sensitive individual. O'Donovan[118] presented a four-year-old girl with infantile eczema and a background of allergy. During hospitalization the child's condition became worse and an electro-encephalogram was made. The record was diagnostic of idiopathic epilepsy. There was no familial background of epilepsy.

Allergists who treat infantile eczema see an occasional case of exfoliative or bullous dermatitis in infants which becomes generalized and which fits into the category of either Ritter's or Leiner's disease. A study of these two conditions is presented by Cole et al[23] with a demonstration of the microscopic findings in both conditions. Sulzberger (p. 449) in a discussion of this paper differentiates the two as follows: Ritter's disease (dermatitis exfoliativa infantum) usually occurs from the second to the fifth day of age. The course is acute, usually a few weeks, and in 90 per cent is fatal, at least before the advent of the modern antibacterials. The disease may be endemic with impetigo and other pyodermas. Bullae are common; Nikolsky's sign is characteristic and the patient looks scalded, with red, moist areas. The patients respond to modern antibacterials according to recent reports. Leiner's erythroderma desquamativa occurs usually from the twentieth to the sixtieth day of birth. It is more chronic and goes on for months. It has a lower mortality; probably 30 to 80 per cent is a fair estimate. This occurs almost exclusively in breast-fed infants

and a question of nutritional deficiences may be raised. Bullae are absent as well as Nikolsky's sign. The appearance is that of greasy scales (cradle cap), with diarrhea and gastrointestinal inflammation. Casein with raw liver and low fat is sometimes effective. The best morphologic distinction, in the reviewer's opinion, is to think of Ritter's disease as a type of impetigo herpetiformis and Leiner's disease as extensive seborrheic dermatitis.

Two patients are presented by Friedman and Zarafonetis[56] having a background of atopic dermatitis and in one instance atopic cataract of the left eye and later lymphoma. One patient had a clinical diagnosis of mycosis fungoides and a microscopic diagnosis of "reticulum cell sarcoma." Since this is a very rare complication of atopic disease one of the discussers (Morris, Boston) wondered whether the previous diagnosis of atopic neurodermatitis in these cases was correct. Improvement of the patients was noted with the use of potassium para-aminobenzoate. The rationale for the use of this preparation stems indirectly from the discovery that PABA increases cellular metabolism greatly. It was decided to try this preparation in leukemia because it was felt that the cells were abnormal and that if the metabolism of these cells could be stepped up, the possibility existed that the cells would not be able to withstand the increased pace of metabolism. Patients with chronic myelogenous leukemia were improved as far as cutaneous infiltrations were concerned when they were given PABA. In these instances KPAB was given in a dose of 18 to 21 gm daily. A convenient way of administration is to take 100 gm of the powder and dissolve it in a quart of water. The preparation is then refrigerated and the dose can be conveniently given in the correct increment starting with lower dosage and in some instances going as high as 24 gm per day. There are other reports in the literature of the relationship between atopic dermatitis and lymphoma. The occasional patient with atopic dermatitis or contact dermatitis may become so severely involved that the disease could be classified as an exfoliative dermatitis. This subject was carefully studied by Wilson[191] who analyzed fifty-four cases of exfoliative dermatitis. Of this group, fifteen had been known to have or thought to have eczema and contact dermatitis. Fourteen had either psoriasis or seborrheic dermatitis which had become generalized. Five of the group belong to some form of reticulosis and ten were considered to have unknown causes. With adequate study the cause of exfoliative dermatitis was discovered in thirty-one patients, and a probable diagnosis was made in an additional nine. The seriousness of the condition is evidenced by the mortality of nineteen in a series of fifty-four.

Lobitz and Campbell[94] studied patients with atopic dermatitis and injected intradermally 0.1 cc of acetylcholine and epinephrine in dilutions of 1 to 10,000 and 1 to 100,000. Isotonic saline solution was the control. The response to epinephrine in these patients was essentially the same as that seen in nonatopic individuals. The authors were particularly interested in the whealing, red flare (axon reflex) and blanching (vasoconstriction). There was a "delayed blanch" in 20 per cent of atopic individuals with the use of acetylcholine. The blanching remained for over sixty minutes in two patients and this was unaffected by procaine. It is suggested by the authors that the delayed blanch from acetylcholine is the result of the direct action of a vasoconstrictor substance on the blood vessels of the skin in the atopic individual. Shelley[167] reviewed the recent research in dermatology centering around the structure of keratin, the formation of melanin,

the problems resolving around hair, apocrine and eccrine sweat. In recent years it has been learned that injuries to the skin may cause damage to the sweat gland apparatus resulting in sweat retention anhidrosis or failure to sweat normally because of occlusion of pores. This can occur after injuries such as sunburn, maceration from sweating or under adhesive tape, irritation from antiperspirants such as aluminum chloride, and damage from local heat or cold. If sweating is stimulated after pore occlusion, anhidrosis occurs in many persons without any other change. The trapped sweat has apparently stoppered the subsequent secretion. In others, however, the sweat breaks through the duct and continues to be formed and to flow into the skin instead of onto the surface. This sweat may escape at various levels in the epidermis or dermis, and the clinical signs accurately reflect the level of rupture. The skin may return to its former normal cycle of keratinization since, in a few weeks, the occluding keratin cap is shed, with subsequent restitution of the normal permeable keratinous sieve. In the atopic individual, the sweat retention syndrome, in the reviewer's opinion, contributes to the summer recurrences.

Graham and Wolfe[69] studied thirty-one patients with eczema. The patients ranged in age from seventeen to seventy-five years. The study was prepared to determine the relationship between stressful life situations and exacerbations of the eczema. In discussing stressful situations, two tests of cutaneous vascular function were made during the interviews. The Hardy radiometer measured the skin temperature which reflected the contracted state of the arterioles. Likewise, the tone of the capillaries and venules was estimated by the reactive hyperemia threshold method. Exacerbations of dermatitis occurred in frustrating situations in which the subject felt that he was restrained from following out his own plans. Dilatation of arterioles, capillaries and venules was an important factor in the pathogenesis of the disease. It was suggested that actual dermatitis resulted from trauma to the areas of vasodilatation. The patient's reactions were interpreted as feeling of guilt with self-punishment rather than attempts at adjustment to life's situations. Seitz, Gosman and Craton[161] agreed with the studies of Graham and Wolfe, just quoted. In using thirty-five patients with localized neurodermatitis it was found that neurodermatitic patients tended to express aggressiveness masochistically. Goldblum and Piper[67] found that when two negro patients with localized neurodermatitis were scratched for one hour daily with a special scratching machine that could count strokes and had a controlled pressure, pigmentation in the new site was evident after three days. Inflammation apparently played a minor role since little was produced. Lichenification was produced in sixty to ninety hours of scratching with a pressure of 75 gm and a minimum of 140,000 scratches. The microscopic section of even normal appearing skin after sixty hours of scratching showed pronounced lichenification. Further studies with this mechanism in atopic dermatitis would be of interest.

Brain[14] reported a number of interesting occurrences following the admission to a hospital of a three-year-old child in 1953 with Kaposi's varicelliform eruption. An eleven-month-old baby admitted for eczema about the same time developed the same eruption on the seventh hospital day. At the same time herpetic lesions developed on the forearms of two attending nurses, and the following day another nurse who had attended these patients had similar lesions. Three other children who had been hospitalized for eczema were discharged from the hospital as a precautionary measure, but each returned within a few days with Kaposi's varicelli-

form eruption. Brain pointed out how contagious eczema herpeticum can be. It is to be remembered that at least 70 per cent of adults carry the virus of herpes simplex. It was possible that in this outbreak, a particularly virulent strain of herpes simplex virus was present. Another possibility is the fact that pyogenic cocci may be a factor in the rapid dissemination of an infecting virus by virtue of the spreading effect of hyaluronidase produced by these organisms.

It is well known that vaccination is contraindicated in the presence of diseases of the skin because of the danger of eczema vaccinatum and other complications. During the smallpox outbreak in Glasgow in the 1950's, patients in the dermatologic wards in the general hospital came in contact with two persons in whom smallpox developed. Eighty-four patients were vaccinated successfully by Dewar and Finn[87] on the first or second attempt, but strict precautions were carefully observed. The vaccination area was thoroughly bandaged and communicable disease precautions were followed. Only four complications occurred. Fries, however, stated that vaccination of allergic eczematous children[129] may lead to severe or even fatal generalized vaccinia. No precautions are adequate to prevent the spread of the virus after inoculation into the eczematous damaged skin. The vaccinia virus can be disseminated by the general circulation. Such a risk should be warranted only after intimate exposure of the child to smallpox. Any exposure of the eczematous child to the vaccinia virus carries a high risk, whether by injection, scarification, or even contact with other freshly vaccinated persons. Exposure to freshly vaccinated persons is responsible for the varicelliform eruption described by Kaposi and seen predominantly on atopic eczematous skin.

Papers on the use of ACTH and cortisone in atopic dermatitis will be found under the heading "Corticotropins and Steroid Hormones."

Beinhauer[8] treated 145 patients with twenty-three pruritic dermatoses. including atopic dermatitis. The patients were given 250 mg of procaine hydrochloride and 150 mg of ascorbic acid. The initial dose was two capsules followed by one capsule every three hours for two days. The third day six capsules and thereafter four capsules daily were given. The patients were treated from four days to eight weeks. When the response was favorable, complete or temporary relief was seen within four days. Headache, dizziness, nausea, vomiting and drowsiness occurred in 8.2 per cent of the patients, and these symptoms were promptly controlled by withdrawal of the medication and sometimes did not recur on readministration of the drug. There was no evidence of drug sensitivity in this series. Procaine given orally produced complete relief of itching in 22.2 per cent of patients and temporary relief in 27.9 per cent. The drug failed, however, in almost 50 per cent of patients. The most favorable response was seen in penicillin urticaria, herpes zoster and in patients who complained of burning tongue. It was felt that the drug is worthy of a trial of therapy when everything else fails. An improvement of the original method was suggested by Rein,[8] consisting of a combination of procaine hydrochloride with ascorbic acid. Each yellow scored tablet contained 300 mg of procaine hydrochloride and 150 mg of ascorbic acid. Patients were advised to take one tablet every three hours. The side effects were negligible. Best effects were obtained in patients with dermatitis venenata and urticaria due to penicillin. Patients with general neurodermatitis were not helped. Lubowe[98] evaluated hexylcaine ointment (2 per cent) dispersed in a water washable cream in the relief of pruritic derma-

toses in 258 patients over a two-year period. A 2 per cent hexylcaine lotion and zinc oxide talc, glycerine and ethyl alcohol emulsion were also used. There was no cross-sensitization between hexylcaine and eighteen patients known to be sensitive to benzocaine or paraphenylenediamine. Relief of itching was obtained in 220 of 258 patients. Lubowe concluded that hexylcaine lotion and ointment are useful and have an extremely low sensitization index. He noted, however, that with the widespread use of these preparations some sensitizations probably will occur.

Nance[115] used preventive treatment for infantile eczema. He inquired into the family history of all newborn infants and considered each one with an allergic family history as a possible eczema problem. Breast feeding is encouraged whenever possible, especially in allergic families, and no infant under the age of three days is given an artificial formula. Complementary foods are avoided under the age of three months. New foods are added one at a time and in small amounts. Mixtures of foods and mixed cereals are avoided. The most recently added food is immediately stopped if eczema occurs. In this event, only milk or milk substitutes are used as a basic diet. He thought that the intestinal wall is more permeable to unchanged protein in the first two days of life than it is later on. Church[21] suggested the following management of infantile eczema. He condemned the use of any restraints in children and suggested sedation and nocturnal isolation of the infant to insure freedom from an oversolicitous mother and to free the remainder of the household from insomnia. He suggested further the use of hypnotics at night for the mother whose demoralized state is partially caused by sleepless nights. Parents are persuaded to ignore the eczema and the scratching. The avoidance of soap and water on the affected areas is suggested, since a dirty child is preferable to an eczematous one. Tar in the form of lotion or paste is the local and least important treatment. In those cases in which scratching is an established reflex, an occlusive dressing in the form of Unna's boot bandages may be all that is necessary.

Eighty-eight patients with various eczematous dermatoses were given high doses of vitamin D_2 by Schnitzer.[159] The patients were given a total of six intravenous injections of 600,000 units of vitamin D_2 hydrosol (Vi-De hydrosol). The injections were given every second, third or fourth day. Complete cure or improvement was noted in sixty-eight of eighty-eight patients with various eczematous dermatoses. The treatment was not effective in seborrheic dermatitis and in neurodermatitis. Vesicular and oozing dermatoses improved within a few days and chronic eczema improved so effectively that topical therapy controlled the condition. Untoward effects included facial congestion, dyspnea, a feeling of anxiety and depression probably the result of nonspecific histaminic action. Exacerbations noted between the second to the fourth, or the eighth to the twelfth day may also have been due to histamine. High doses of vitamin D are contraindicated in patients with latent tuberculosis, active focal inflammations, advanced arteriosclerosis and/or renal disease. The administration of high doses of vitamin D raises low calcium blood levels and the calcium content in the tissues is increased. The mode of action of this beneficial effect not only in various eczematous dermatoses but also in lupus vulgaris is not known. Many dermatologists use calcium intravenously for acute dermatoses. Kyle et al[91] investigated the mineral alterations resulting from the intravenous administration of calcium. Elevation of serum calcium persists for less than twenty-four hours and is accompanied by a rise in serum phosphorus. Subjects without bone

disease retain approximately 60 per cent of the infused calcium, the remainder being rejected in the experimental dog. Rein and Goodman[142] presented a series of sixty patients with various pruritic dermatoses, in whom for the most part a tension factor contributed to the cutaneous disorder. Of this group nineteen had atopic dermatitis. The dosage was 0.25 mg four times a day for one month. Forty of the sixty patients experienced definite relaxation and tranquilization, and slept better. No significant blood pressure or pulse changes were noted in this essentially normotensive group. Side effects were noted in ten patients and these consisted of nasal congestion, increased appetite, depression, dreams, nocturia, dyspnea, weakness and nausea.

Using group psychotherapy, Guy and co-workers[72] studied twenty-five atopic eczema patients over a period of eighteen months. It was found that group psychotherapy modified to meet the special needs of a relatively homogeneous test group of female patients with atopic eczema has proved to be an effective method of treatment. The authors used limited selection of their female atopic patients and were able to establish a satisfactory relationship between the dermatologist, psychiatrist and group of patients in a common setting. Individual psychotherapy was reserved for some patients. Therapeutic success depends on the physician's ability to cope with the excessive demands and the well-known unresponsiveness of this group of patients. Remissions of atopic eczema occur when frictional dependency ties are severed, compensatory emotional support is gained and infantile wishes find greater satisfaction in aggressive outlets. The reviewer notes that the discussers of this paper offered favorable comment and agreed in the main with Guy et al. In contradistinction, if this paper had been presented ten or fifteen years ago, a storm of protest by the discussers would have arisen. It would seem that dermatologists as a group are becoming more tolerant to the application of psychotherapy, individual or group, to this class of patients. They agree that deep psychotherapy has no place in the average case. It is one of the interesting facets in an involved problem which encompasses the fields of dermatology, allergy and psychiatry.

URTICARIA

Advances in our knowledge of the fundamental mechanisms involved in the production of urticaria and its related vascular cousins have been scattered and few. One outstanding contribution considers the "vexing problem of urticaria." In an exhaustive article, Sheldon et al[166] presented a modern procedure for handling patients with urticaria and incorporated the information selected from 445 references. After a discussion of background material on etiology and pathologic physiology, they considered the four factors which should receive special consideration while a thorough initial history is taken. These are drug allergy, food allergy, infections and psychic factors. The treatment of urticaria and angioedema is simple if an etiologic diagnosis can be made. In many cases, however, symptomatic therapy is needed. The steroids, the antihistaminics, epinephrine and ephedrine preparations are the drugs of choice. Numerous "nonspecific" methods of treatment are mentioned.

Siegel and Bergeron[172] were interested in obtaining data as to the etiology of urticaria and angioedema in a consecutive series of children and young adults with particular reference to the role of infection. They were also interested in seeing whether there were any electrocardiographic findings

during acute phases of urticaria and angioedema. They studied 115 patients with acute and chronic urticaria. The adults were thirty-four years of age or younger. In the series were forty children ranging in age from two months to nine years. The authors felt that they could incriminate foods in fourteen cases, drugs (including penicillin) in twenty-eight cases, with nine other drugs involved; twelve patients had infection problems; three physical allergies; ten psychosomatic problems; three insect problems. In thirty-six, however, roughly a third of the patients, no etiology could be found. Very little change in the electrocardiogram was noted in this entire series. The absence of electrocardiographic changes in ninety-eight patients in this study indicates that cardiac abnormalities reported in serum sickness and drug eruptions probably are rare. Pirilä[127] reported a case of urticaria due to sulfur dioxide and a case of dermatitis due to hydrogen sulfide. Both of these allergic sensitizations were due to substances in polluted air, and exposure to as little as 0.0012 to 0.0015 volumes per cent of hydrogen sulfide was sufficient to cause reactions. Both patients were free from symptoms when they were out of the sulfur environment.

Fisher and Schwartz[53] studied 100 patients with subacute or chronic urticaria and 120 controls, of whom twenty patients had severe dermographism. In 100 patients they found that if the eruption had been present at least three weeks, the incidence of dermographism was 6 per cent. A possible allergic mechanism for urticaria was demonstrable in 19 per cent of this group. Of twenty patients with severe dermographism without urticaria, none gave evidence that an allergic mechanism was involved. The authors pointed out that dermographism is often confused with chronic urticaria, and various accepted modes for the approach to urticaria which include elimination diets and allergy studies are useless in dermographism. The question of the pathogenesis of dermographism brings the following comment in the *Journal of the American Medical Association.*[137] Dermographism is not a true allergy since no allergen or antibody appears to be involved. It is apparently due to an excessive release of histamine from the tissue cells as a result of minor trauma. A similar phenomenon occurs with a major stimulus in normal persons. As a rule, antihistamine therapy is helpful in dermographism. Many years ago Duke suggested rubbing the skin vigorously with a stiff brush at daily intervals or perhaps oftener. The improvement noted by this technique is probably the result of the depletion of available histamine. Since mechanical and other nonspecific stimuli can precipitate reactions basically due to allergens such as food and inhalants, it is important to make sure that no true allergic factors are present in patients with dermographism.

A query regarding desensitization for a five-year-old child, who develops urticaria and asthma when she smells fish or when she is in a room in which fish has been fried, is raised in the *Journal of the American Medical Association.*[134] The answer stated that most allergists agree that desensitization to foods by giving injections of the antigen is not successful or practical. Allergy to fish is one of the most violent types of hypersensitivity. Not only would injection of fish antigen be hazardous, but also it is doubtful that the degree of sensitization accomplished would be sufficient to influence the clinical symptoms. Prevention was the best method of avoiding difficulty and epinephrine, promptly administered, was advised. It was also thought that this sensitivity may persist throughout the patient's life.

A woman, aged thirty-three, was presented by Cipollaro[22] with a history

of having had swellings about the eyes off and on for eleven years. The history revealed that she had had all sorts of allergy and bacteriologic, as well as ophthalmologic, examinations which were essentially normal. She had never been in the tropics. Several x-ray treatments filtered and directed to each side of the face in the region of the zygoma were followed by involution of the swelling. Filariasis had been considered. There was no evidence of a syndrome of intracranial venous obstruction and of arteriovenous aneurysm. Neurologic examination had been entirely normal. An arteriogram had given normal findings, but the possibility of an orbital angioma was still considered. The patient was presented for further suggestions as to etiology and therapy. This discussion developed the following points. Sarcoidosis and dermatomyositis occasionally produced this type of symptomatology. In addition, it was suggested that the patient be studied for the lupus erythematosus phenomena. Localized myxedema of the orbit may occur with or without cutaneous lesions. This case history is presented to show the ramifications of investigation for a patient with angioneurotic edema in the periorbital areas.

Stevens-Johnson syndrome is a polymorphous eruption having elements of urticaria, vesicles and bullae. Mauriello[105] analyzed fourteen patients with Stevens-Johnson syndrome, who were seen during an eighteen-month period at the United States Army Hospital at Fort Dix, New Jersey. The condition has a number of names and has been variously reported as eruptive fever with stomatitis and ophthalmia, Behçet's disease, Reiter's disease, and in one instance it was called mucocutaneous-ocular syndrome. Because the disorder affects the eyes, mouth, skin and genitalia, it may be seen at the onset by either an ophthalmologist, dentist, otolaryngologist, dermatologist or urologist, in addition to the patient's family physician. The condition may be an expression of allergy or hypersensitivity, since there seems to be a relation, at times, to drugs such as aspirin, barbiturates, sulfonamides and phenolphthalein. Viruses of various disorders have also been incriminated. The patients in this series were treated with antibiotics and intravenous ACTH. Most of them received corticotropin by intravenous drip using 20 mg daily. One patient received 40 mg daily. Mauriello was of the opinion that the use of corticotropin and cortisone is of questionable value in these patients not critically ill. The reviewer notes that a seriously ill patient with Stevens-Johnson disease responded in a very satisfactory manner to high dosage with ACTH. This is on the order of 60 to 80 mg intravenous daily for a short period of time. Dermatologists do not hesitate to give this high dosage in patients with pemphigus or disseminated erythematosus. Since this disease may terminate fatally (Finland et al, Am. J. Med., 4:473-492, Apr., 1948), adequate dosage of corticotropin should be given due consideration.

Erythema annulare centrifugum is an inflammatory skin eruption having, as the name implies, an annular configuration, and morphologically is closely allied to urticaria. Jillson[82] has been able to show that at least some cases of erythema annulare centrifugum are dermatophytids. One week after *Trichophyton* was injected, both within and outside a lesion, the inner site was represented by a fading macule, whereas the *Trichophyton* test outside the lesion had enlarged to produce a miniature replica of erythema annulare centrifugum. This agrees with the finding of Epstein and Grummandel in 1930, who showed that, in ringworm in human subjects, the center of the resolving infection had a fair amount of local immunity different from areas outside of the ring, which were susceptible

to infection. All this was reproduced by Jillson in a patient with this condition. He pointed out that a positive *Trichophyton* test must be present to make a diagnosis of dermatophytid and the response to *Trichophyton* must be of the same clinical and histopathologic appearance as the type of dermatophytid present. There are rare exceptions to this rule. In eczematous dermatophytids of the hands a tuberculin type of reaction is found. It is further believed that milder forms of erythema annulare centrifugum are commoner than are stated in the literature. The lesions are asymptomatic and usually located on the covered parts of the body. They are usually associated with superficial onychomycosis and tinea pedis. The lesions on the trunk disappear when the primary focus is attacked with antifungal agents. Ellis and Friedman[43] concluded that erythema annulare centrifugum (Darier's disease) has been reported under a variety of names, but clinically the picture may be fairly characteristic, showing annular plaques which migrate slowly; the lesions may show some scale or very superficial crusts at the active borders; and there is no definite predilection as to age and sex. Urticaria with an annular configuration is a fairly descriptive term, but the scaling and superficial crust would easily differentiate the two. The authors found that while the clinical condition may be variable, the histologic picture from a study of fifteen cases is characteristic. Clinically, the condition has been ascribed to id reactions due to epidermatophytosis, breast cancers, infections and other diseases. Robbins[144] reported an interesting variant of urticaria pigmentosa with bullae and vesicles. The patient was a six-months-old white girl with lesions of one and one-half months' duration. The biopsy verified the diagnosis and the eruption was controlled by the use of ACTH gel and Benadryl® elixir. This is a rare variant.

DRUG ERUPTIONS

Severe and at times fatal drug reactions to penicillin were extensively reported in last year's Progress of Dermatologic Allergy.[58] There is a noticeable reduction in these reports in this review. Perhaps the notoriety given to penicillin over the past two or three years has been productive of the use of caution on the part of the penicillin injectors. New drug formulations and allergic manifestations to these preparations have forced penicillin reactions into the background. Dameshek[33] presented a brief review and a classification of drug allergy from the standpoint of the hematologist. He classified the following drugs as white cell granulocyte reactors: aminopyrine, Novaldin,® Causalin,® dinitrophenol, sulfapyridine, thiouracil, propylthiouracil, Tapazole® and Butazolidin.® Leukopenogenic effects have also been produced by Pyribenzamine® and Antergan.® Streptomycin and chloromycetin also fall into this group. Red cell reactors include phenylhydrazine, sulfanilamide, naphthalene, p-dichlorbenzene and acetanilid. Platelet reactors include Sedormid® and quinidine. In this connection, from work in his laboratory, he feels that there is no question that quinidine thrombopenic purpura, like that due to Sedormid, is immunologic in nature and that the immunization mechanism can actually be demonstrated by *in vitro* tests. Total bone marrow reactors include benzene. Benzedrine,® Tridione,® Mesantoin,® Dilantin® sodium, Atabrine® and chloromycetin. He also discussed the antileukemic and antileukosarcoma drugs which include nitrogen mustard and triethylene melamine (TEM). Almost all of the various drugs showing hemotoxic activity have a central benzene ring structure and a varying number of associated N, NH or NH_2

groupings. Increase in drug sensitivity is due not only to the various new synthetic preparations available but also to the habit of prescribing a potent pharmaceutical for every slight sniffle, every tiny rise in temperature, every ache and other vague symptom. Furthermore, the patients are surrounded with popular articles, radio talks and television broadcasts extolling the miracles of modern medical practice, and they in turn demand numerous potent medications. Every home medicine closet probably contains a potential "keg of dynamite." The reviewer notes that this is a refreshing attitude coming from an eminent internist and hematologist. In addition, Dameshek[34] presented experimental and other evidence to indicate that there is a possible interrelationship between leukemia and the use of certain agents which include dermatologic, therapeutic tars, phenols, chrysarobin and superficial x-rays. Patients who come in contact with benezene, rubber cement, paint remover, arsenicals and insecticides should have occasional blood counts, and if these are at all abnormal, their occupational duties might be curtailed or otherwise modified. The author pointed out that the number of new synthetic drugs that have as their central basis a benzene-ring structure linked to an NH_2 (amino) group. NH or N is legion, and before any of them is used it might be wise for the physician to glance at the formula. The anti-epileptic drugs (Dilantin, Mesantoin and the like), the antihistaminics, Dexedrine® and even the antibiotic chloramphenicol have one or more of these groupings, which in one way or another seem to be toxic to the bone marrow. What is toxic to the marrow may also be leukomogenic. Hoigné and co-workers[80] recorded the thrombocyte agglutination reaction in twenty-five patients sensitized to twenty-eight drugs. The reaction was positive in twenty-seven of twenty-eight known allergic reactors. The reaction was negative in over fifty controls. There was a strong parallelism between thrombocyte agglutination reaction and a decrease of thrombocytes in peripheral blood after exposure to the antigen. Most of the patients in this series had manifestations of drug allergy characterized by granulocytopenia, drug fever, and so forth. There was a minimum of skin reactors, such as urticaria or purpura, in this group.

Engleman et al[44] presented a number of patients who were given phenylbutazone. All six patients were women who had no known antecedent liver disease, except the patient in Case 1 who had jaundice for four days fifty-nine years previously. The temporal relationship between the administration of phenylbutazone and the onset of hepatitis was noted. Jaundice appeared six to forty days after the ingestion of the initial dose of the drug. Other causes of hepatitis were ruled out. It is concluded that phenylbutazone is potentially hepatotoxic. Cone et al[26] reported a case of a forty-four-year-old housewife treated for arthritic pains in the wrist, fingers and low back, which had been present since March, 1953. The patient had been given fifty tablets of phenylbutazone, of 100 mg each, to be taken over a two-week period. On October 9, 1953, five days after she had completed this course of treatment, she complained of soreness of the mouth and eyes of one day's duration. The arthritic symptoms had improved. The following day a generalized nonpruritic skin eruption developed for which she was hospitalized. By the third hospital day a marked extension of the eruption developed in which there was a prominent bullous component, and the eruption had become generalized. In spite of corticotropin, cortisone, antibiotics, plasma and local therapy, the condition became more toxic and the patient died on the fourteenth hospital

day. At postmortem examination, the findings of a probable staphylococcic septicemia with almost no polymorphonuclear response suggests the importance of vigorous antibiotic therapy in this type of problem. Archer and Kantor[3] reported the tenth case of agranulocytosis following the use of phenylbutazone. A forty-three-year-old white woman who was being treated for arthritis with phenylbutazone developed severe sore throat and fever on the seventeenth day of medication. The drug was discontinued. The blood picture and bone marrow showed the characteristic picture of the lymphoid form of agranulocytosis. She recovered with symptomatic treatment. The authors concluded that there is no way of predicting which patient will develop serious complications when given phenylbutazone. Other reports of agranulocytosis due to Butazolidin were made by Stifel and Bernheimer,[176] Bershof and Oxman,[11] Werblow and Neber,[189] and Etess and Jacobson.[46]

Wechsler[188] reported the case of a fifty-six-year-old white woman with controlled diabetes and asymptomatic arteriosclerotic heart disease, who experienced a sudden onset of paroxysmal auricular tachycardia for which she was given quinidine sulfate 0.4 gm three times daily after a test dose. After the medication had been taken for three months, a pruritic lichen planus-like eruption developed on the dorsa of the hands, forearms, legs and neck. The eruption was intensified by exposure to sunlight and subsided without untoward effect when the quinidine was discontinued. Parmer and Sawitsky[124] reported the case of a thirty-six-year-old woman who was found to have discoid lupus erythematosus in 1950. In August, 1952, oral administration of quinacrine was started. Two weeks later the skin lesions were improved, but five weeks after the onset of treatment the patient complained of generalized aching and this was followed in four months by fever, vaginal bleeding and hemoptysis. Despite therapy, the patient died of fatal aplastic anemia following hospitalization. Although millions of servicemen were given this drug in the form of atabrine or one of its analogues, Parmer and Sawitsky postulated that an allergic reaction may occur more often in patients with certain chronic skin diseases than in the general population. Aplastic anemia was a very rare finding in military personnel.

Asch[4] reviewed the literature of reactions following bronchography with iodized oil and found twenty-one nonfatal and nine fatal cases of acute iodism following this procedure. Chloriodized oil contains 27 per cent iodine and 7.5 per cent chlorine organically combined with a highly refined peanut oil. A fifty-three-year-old white man developed chest pain and localized areas of edema in the skin two days after bronchography with this agent. He also had generalized aches, malaise, dyspnea and hemoptysis. This was accompanied by a temperature of 100.4° C. In addition to the angioedema, he developed acneform lesions with central necrotic areas. Roentgenograms showed an interstitial pneumonitis. The blood contained 65 micrograms per 100 cc of serum iodine, and it was suggested that there was absorption of iodine possibly by swallowing during the procedure. The patient recovered with symptomatic treatment. Simon et al[173] reported that reactions to Diodrast® and similar preparations occasionally are serious enough to be called to the attention of the allergist. Up to 1949, twelve deaths have been reported in the literature. Mild reactions consist of chills, flush, arm pain, nausea and vomiting, and urticaria. Severe reactions consist of edema of the eyelids, laryngospasm, bronchospasm, vertigo, pallor of the skin, syncope, cyanosis and shock. The author's experience

with intradermal and eye sensitivity tests has only served to emphasize their futility and lack of reliability. Patients with a history of allergy are much more likely to react to contrast media. The authors studied 500 cases in which 10 mg of Chlortrimeton® was added to the contrast media. The incidence of allergic reactions was reduced from 17.3 per cent to 7.1 per cent. Epinephrine and other antihistaminics should be available in the event of a reaction. The reviewer has witnessed several of these unfortunate severe reactions resulting in sudden death. Suggestions for management include intubation apparatus, suction and oxygen, with an operator competent to handle these life-saving modalities. A prepacked emergency kit with suitable drugs and plasma augments the mechanical aids.

Prolonged therapy with large doses of hydralazine (Apresoline®) has been reported to produce a syndrome resembling several forms of collagen diseases. Reinhardt and Waldron[143] reported that this syndrome progresses from mild arthralgia to a clinical picture of rheumatoid arthritis and finally simulates disseminated lupus erythematosus. The authors presented a further report of a forty-eight-year-old negress treated for hypertension with Apresoline. This patient exhibited not only the clinical picture of rheumatoid arthritis and disseminated lupus erythematosus but also pathologic evidence of these diseases. In an additional case report along this line, Shackman et al[162] presented the case of a fifty-nine-year-old white, married, nulliparous woman who was treated for hypertension with Apresoline (hydralazine). In this case, too, a clinical and laboratory picture mimicking acute disseminated lupus erythematosus was found. The Apresoline had been given over a period of nine months. There was complete regression of all clinical signs and symptoms and all laboratory findings within one month of the discontinuance of therapy with this drug. Perry and Schroeder[125] presented a small series of patients who were given hydralazine for the control of hypertension and who developed symptoms consisting of arthralgia, rheumatoid arthritis and, in severe cases, a group of symptoms indistinguishable from disseminated lupus erythematosus. Abnormal cephalin-cholesterol flocculation and thymol turbidity are helpful diagnostic aids. The condition regressed in all patients when the use of the drug was discontinued.

A number of reports have appeared in the literature testifying to untoward reactions particularly in allergic individuals who are given intravenous Decholin® for the determination of circulation time. Sanchez and Morris[156] presented four new cases with untoward reactions to Decholin, and recorded two patients who died. These four untoward reactions are of interest because there apparently was no background of hypersensitivity. The authors concluded, however, that those patients with a history of allergy and those with right to left shunts may be particularly vulnerable to the untoward effects of sodium dehydrocholate.

Thirty-one cases of blood dyscrasia from chloramphenicol were reported from the British Isles, and twenty-eight of the thirty-one were classified as aplastic anemia. Of the thirty-one cases, twenty-four have so far proved fatal. Hodgkinson[79] also found that in twenty-four of the thirty-one cases the dosage administered was in excess, and the average was over double that of a dosage calculated to be the maximum necessary to control most infections, and over four times that commonly used. It is suggested that in adults a total dose of 26 gm should not be exceeded. In children the total dose should not exceed the equivalent of 100 mg per kilogram of body weight daily for seven days. The length of treatment

should not exceed ten days. Olansky and Janney[119] studied thirty-four patients treated with chloramphenicol for various infections. He found six reactions, two of the severe type and four less severe but distressing. The reactions were characterized by skin changes of the anogenital regions and the mucous membrane of the mouth resembling a vitamin B complex deficiency. It was decided, therefore, to give intramuscular injections of 1 cc of vitamin B complex daily during therapy. He concluded that intramuscular injections of vitamin B complex apparently prevent reactions of the mucous membrane to chloramphenicol. Vitamin B complex intramuscularly apparently has therapeutic value in the treatment of these reactions only if given early.

A fifty-three-year-old negro, a cardiac patient, was given tincture of digitalis. Urticaria, angioedema and the formation of bullae in the skin followed. Specific skin-sensitizing antibody to digitalis glycosides was demonstrated by Mosko and Taylor.[114] Although digitalis hypersensitivity is rare, previous reporters had not found a positive skin test. Mechitty[109] observed the occurrence of bronchial asthma and herpes simplex in two tuberculous patients who were receiving streptomycin. Both patients had a chronic form of pulmonary tuberculosis. The side effects appeared during the first week of therapy in both patients. In the second patient administration of streptomycin was resumed and was continued for thirty days with no untoward effect.

Milanés et al[110] studied Enzar,® which is a highly purified crystalline trypsin for intravenous use. The drug may be given intravenously in doses of 125,000 units diluted in 250 cc of Ringer's solution twice a day for ten consecutive days. The infusion rate is 30 to 40 drops a minute. Later the dose was decreased to 50,000 units, with the addition of 10 mg of Histadyl.® Parenzyme in oil, employing 2.5 mg of the enzyme, was given intramuscularly once daily for five consecutive days, then twice a week for a week or two. Side reactions in almost every case following the intravenous use of Enzar included chills, fever, headache, pruritus and, in some patients, urticaria. The use of these agents in chronic ulcerative colitis, as well as in phlebitis, is attended by side effects which may be severe. None of the patients were asthmatic individuals. Since it has been shown by some investigators that these materials will produce hydrolysis of various protein moieties in the clotting mechanism, the release of these proteins may produce allergic reactions in hypersensitive individuals. Makous and Vander Veer[101] reported a case in which Phenindione® was given for thrombophlebitis. The patient, a forty-two-year-old negress, subsequently developed a morbilliform eruption and an acute febrile episode fifteen days after therapy was begun. In addition she showed adenitis, leukemoid reaction, hepatitis and anemia. The skin test to Phenindione was positive although not strikingly so. Passive transfer skin tests were unsuccessful. The oral provocative tests with Phenindione resulted in febrile and systemic response. Similar pictures have previously been described by others to this new anticoagulant.

Toxic reactions of all types using propylthiouracil for the management of hyperthyroidism have occurred in 1.6 to 3.2 per cent of the cases. Severe leukopenia and agranulocytosis have occurred in 0.5 to 1 per cent of patients, and fatalities from agranulocytosis have been reported. Sixteen toxic reactions in the treatment of 214 patients with Tapazole, an incidence of 7.5 per cent, have previously been reported. Levine and Rosenberg[93] presented a thirty-seven-year-old white married woman who

developed agranulocytosis, anemia and thrombocytopenia following Tapazole therapy. Rapid clinical and hematologic improvement occurred after cortisone therapy was begun. There is experimental evidence, however, that cortisone has a deleterious effect on bone marrow regeneration following irradiation and also that it increases the leukopenia following nitrogen mustard therapy in animals. On the other hand, several cases have been reported of rapid and dramatic improvement of drug-induced agranulocytosis when cortisone-ACTH therapy was begun.

Korst[88] stated that experience in the early days indicated that gastrointestinal upsets and occasional eruptions could be produced by 5 to 30 gm of para-aminosalicylic acid per day. Fever, dermatitis and bullous eruptions were also noted. With the longer use of the drug, other reactions, which included urticaria, systemic reactions and blood dyscrasias, were encountered. Recent reviews indicate that significant reactions could be expected in 2.5 per cent of patients treated. In general, the reactions fit into an acquired hypersensitivity pattern which is usually specific to this agent. Reactions subside promptly when administration is stopped, and a milder reaction with an eosinophilia can be obtained by using a test dose of the drug. Patients usually can be desensitized if it is desirable to continue therapy with para-aminosalicylic acid. A history of allergy or other types of drug intolerance does not necessarily indicate that acquired sensitivity will develop. Cross-sensitivity to salicylates should be checked in sensitive patients. Patch testing is not reliable and a test dose of the drug given orally seems to be the most definite means of implicating para-aminosalicylic acid as the drug at fault when sensitivity is expected. Downs[40] reported a woman, aged forty, with moderately advanced tuberculosis, who was given para-aminosalicylic acid three times a day. Ten days later she reported headache, malaise and low grade temperature. These symptoms quickly subsided. She remained normal for about a month, when headache, abdominal pains, vomiting, chills and fever, and generalized dermatitis developed. Administration of the drug was stopped but the eruption continued, with edema and vesicle formation. Subsequently, weakness and irregular pulse developed and an electrocardiogram showed a mild heart block. It was believed that the myocarditis could be explained as an allergic reaction to para-aminosalicylic acid. BAL and sodium lactate seemed to effect a favorable reaction, but these preparations were used late in the disorder.

Rostenberg and Webster[154] reviewed the mechanisms by which cutaneous drug reactions may develop. The main thesis was described in detail when they discussed the mechanisms of penicillin hypersensitivity, reviewed in last year's "Progress in Dermatologic Allergy." It is again emphasized that allergy comprises only one of the possible pathogeneses for drug reaction. An effort is made to clarify the terms intolerance, idiosyncrasy and allergy. The Shwartzman reaction, the Herxheimer reaction, ecologic mechanisms and biotropic mechanisms are discussed. The clinical varieties of drug eruptions are extensively described and a possible explanation of the mechanism is given. Kutscher et al[90] had previously published their work on the reactions in the oral cavity following the use of terramycin, aureomycin and procaine penicillin troches. In this present controlled study a number of patients varying from eighty to 100 with various types of minor oral disorders were used; students were used as controls. The present study included bacitracin, tyrothricin, polymyxin B and gramicidin troches, five per day given for four days.

Reactions to these medications ranged from 8 per cent to 12 per cent in the treated group. Many of these reactions were of minor significance. They compared favorably with previously reported percentages; for terramycin 53 per cent, aureomycin 51 per cent, and procaine penicillin G 38 per cent. Despite the minimal number and slight severity of reactions accompanying therapy with antibiotic troches, it is suggested that these agents be utilized when their administration is specifically indicated and the promiscuous use avoided.

Morris[113] studied thirty patients who showed redness, vesiculation, papules, moisture, scaling and pigmentation particularly in the anogenital areas immediately following the use of antibiotics which included penicillin, oxytetracycline, chlortetracycline or streptomycin. In three patients the eruption appeared as a direct result of exposure to the sun's rays with probable photosensitization. In twelve patients diarrhea was present and in five a coexisting inflammatory dermatitis of the mouth (stomatitis) was present. In all patients, the administration of nicotinic acid by mouth, 100 mg three times a day, resulted in the disappearance of the eruption in twelve days or less. The author suggested that most antibiotics may inhibit the utilization of the amino acid tryptophan or prevent its conversion to niacin or both. This would explain the deficiency in the improvement with the use of this agent.

It is well known that a multiplicity of side symptoms arises in many patients receiving intensive antibiotic therapy, who are usually very ill. Vaginitis, dermatitis, cheilitis, pruritus ani, gastroenteritis and stomatitis are seen. These symptoms have been attributed to the finding of increased numbers of *Candida albicans,* and the question of hypersensitivity in patients with depressed resistance arises. In addition, there are increases in the number of *Staphylococcus aureus, Proteus* and *Pseudomonas* among other organisms which are being incriminated. Robinson[146] concluded that *Candida albicans* is found as part of the normal intestinal flora in 16 per cent of normal persons. The incidence of this organism is not influenced by the administration of penicillin or the broad spectrum antibiotics. *Candida albicans* is found in the vaginal tracts of up to 15 per cent of normal pregnant women. The oral pharynx of normal persons contains 14 per cent. It is suggested that the reactions attributed to *Candida albicans* are not causative. The development of moniliasis is the result of lowered resistance to the invasion of *Candida albicans* and not of antibiotic therapy. Turell and Maynard[185] studied a number of patients who presented side effects of antibiotic therapy and found that the anorectocolonic side effects were not of a serious nature. Local therapy controls the perianal skin irritation, and usually most patients recover spontaneously. They found that acidophilous milk (yogurt) or buttermilk, or both, as a sole form of treatment was completely ineffective in controlling either diarrhea or pruritus.

Surdakowski[180] reported the case of a twenty-eight-year-old white woman who was admitted to the hospital with chills and fever, edema of the ankles and scattered tender areas over the dorsa of the feet. History revealed that she had taken forty tablets of penicillin orally three weeks before admission. She was given further penicillin intramuscularly on the third, fourth and fifth day of her hospital admission and this was followed by an exacerbation of her old lesions and the appearance of new lesions over both anterior tibial areas. Biopsies revealed a typical pathologic picture of periarteritis nodosa. This patient made a complete recovery after discontinuance of penicillin.

Reichlin et al[141] reported the case of a twenty-six-year-old man treated for syphilis twice weekly with injections of procaine penicillin in sesame oil, with aluminum monosterate. Transient local swellings and urticaria developed which were not troublesome when an antihistaminic was added to the penicillin injections. Finally, after a further injection of penicillin a dry, sore throat and a burning paroxysmal cough, chills and fever developed which required admission to the hospital. Chest film showed diffuse mottled infiltration throughout both lung fields. Subsequently, the blood eosinophils reached 80 per cent, the total white count was 42,900 per cubic centimeter and a diagnosis of Loeffler's syndrome was made. Intradermal tests with procaine penicillin and scratch test with the vehicle, sesame oil, and aluminum monosterate gave negative skin reactions. Collins-Williams and Vincent[25] noted that only three definite penicillin reactions were observed in a large pediatric hospital with almost 20,000 in-patient and almost 100,000 out-patient admissions. There were no cases of anaphylactic shock. A few minor reactions or probable reactions were noted. Two hundred children, two-thirds of whom were nonallergic, were tested with aqueous penicillin. Two positive reactors were found in the nonallergic group and one positive reaction observed in the allergic group. Skin tests were equivocal, and the author concluded that skin testing with penicillin does not seem to be a worth-while procedure for routine clinical use.

An interesting case of anaphylaxis resulting from penicillin ophthalmic ointment was reported by Carter and Cope.[20] A woman, aged forty-four, had received about 5,000 units of penicillin in 1946 without side effects. Seven years later she was given an injection of penicillin for bronchitis, which was followed by tightness in the chest, wheeze and dyspnea together with a cutaneous eruption. Three months later she applied penicillin ophthalmic ointment, containing 100,000 units of crystalline potassium penicillin per gram, to an inflamed eye. Within a few seconds there was an offensive taste in the mouth. This was followed shortly by dyspnea, flushing, lower abdominal pain and passage of a large watery stool. Symptoms were controlled by 0.5 cc of 1 to 1,000 epinephrine, 1 grain of Luminal,® 0.4 mg of atropine sulfate and 100 mg of Pyribenzamine. Five months later a patch test with the penicillin ophthalmic ointment was positive and there was a whealing reaction in the skin, with several small pseudopodia which developed in thirty-five minutes. Rosenthal[149] recorded that the office of the chief medical examiner of the City of New York reported eight instances of sudden death following the injection of penicillin. Autopsy findings were available in six of the eight cases. In none of the cases was there any penetration of a vessel by the needle used to inject the penicillin. It was thought that the penicillin was the active sensitizing agent rather than the procaine radical incorporated in the penicillin. Reports of fatal and nearly fatal reactions to penicillin are rapidly increasing and demonstrate the ever mounting importance of the problem of penicillin sensitivity. Bell et al[9] added a number of case reports with fatal reactions and severe reactions from the use of procaine penicillin. Some of the reactions in man resembled symptoms shown by cats which were given injections of procaine penicillin. The median lethal dose of procaine penicillin given intravenously to cats is about 100,000 units per kilogram of body weight. It is inferred from the personal experience in man and with the experimental work done in cats that accidental intravenous injection of suspensions of procaine penicillin is the cause of some of the severe or fatal reactions in man. It is suggested

that the precaution be taken of introducing the needle into the muscle without the use of the syringe to see whether a blood vessel has been tapped. They reported that this happens about once in fifty injections even in the most skilled hands. If blood appears, the needle is withdrawn and reintroduced elsewhere. If no blood appears within twenty seconds, the syringe is attached and the injection made. It is felt that if the same needle is used in withdrawing suspensions of procaine penicillin into the syringe that is used for the intramuscular injection, the needle may become blocked, thus preventing the appearance of blood when a vessel is tapped. Hence, if a dry needle is used for the intramuscular injection before the syringe is attached, this possibility is avoided.

CORTICOTROPINS AND STEROID HORMONES

Selected Experimental Studies—Williams et al[190] studied the relationship of steroids to the reactivity of small blood vessels. A variety of inflammatory stimuli and steroids were also investigated. The reactivity of arterioles to norepinephrine and histamine before and after cortisone was observed using the rabbit ear chamber technique. These experiments confirm the fact that cortisone increases vessel tone in the normal animal. It was found that cortisone had no consistent effect on arteriolar response to norephinephrine in normal animals, the threshold of response usually being the same as in controls. There was no evidence that responsiveness to norepinephrine increases with cortisone treatment. Because intravenous injections of small doses of histamine into normal rabbits produce variable and irregular responses in the arterioles, it was difficult to evaluate the effect of cortisone on these responses. In human beings, cortisone has no effect on the cutaneous histamine response. From other data it could be concluded that cortisone in rabbits, at least, inhibits the capillary permeability induced by histamine, but appears to have no clear-cut effect on arteriolar response to histamine. Vasoconstriction of the capillary bed by cortisone was noted in the hamster's cheek pouch by Wyman et al.[195] These were *in vitro* observations using direct microscopy.

Kramar et al[89] noted that recent clinical observations and experimental work suggest that capillary resistance is not only a local phenomenon but subject to hormonal regulation. The adrenal cortex is principally involved and cortisone is its mediator. In rheumatoid arthritis the rise in capillary resistance was consistently accompanied by a decrease in the eosinophils. Nonspecific stress, such as x-ray irradiation, nitrogen-mustard or fever therapy, as well as epinephrine or insulin, had a similar effect. In laboratory animals, the authors were able to demonstrate an inverse correlation (persistent high capillary resistance and a persistent low eosinophil count) in any situation in which a high cortisone level was maintained during a long period of time by either exogenous (cortisone administration) or endogenous method (protracted stress).

The effect of cortisone and adrenocorticotropic hormone on passively transferred delayed hypersensitivity to 2, 4-dinitrochlorobenzene in guinea pigs was studied by Seebohm et al.[160] Cellular exudates from guinea pigs sensitized to 2, 4-dinitrochlorobenzene were sedimented by centrifugation, resuspended in Locke's solution, counted, and then injected intraabdominally into guinea pigs. The donor animals were then treated with corticotropin, 25 mg daily in three doses, and cortisone, 25 mg daily in divided doses. Corticotropin and cortisone suppressed the cellular reaction to intraperitoneally injected mineral oil by approximately 50 per cent.

Corticotropin suppressed the sensitivity given to passively sensitized guinea pigs, but cortisone did not. It is possible that the adrenal stimulating effect of corticotropin causes the production of a hormone or hormnes different from cortisone. There is also other evidence to suggest that milligram for milligram, corticotropin exerts a much greater effect than cortisone.

Sixteen patients who were sensitive to compounds of the para group, as well as Phenergan, penicillin, rubber, cocaine and turpentine were studied by Sidi and Bourgeois-Gavardin.[170] A 2.5 per cent hydrocortisone ointment was applied at variable times before and after patch testing. The results were contradictory, but it was concluded that hydrocortisone ointment had no inhibitory effect on the reactions of strongly hypersensitive patients. In eighteen patients sensitive to a number of common patch antigens, an injection of a 0.125 cc solution of hydrocortisone acetate intradermally into the normal skin of the back before a patch test was made resulted in complete inhibition of reaction to the patch test in ten, partial in seven and had no effect in one. The zone of inhibition was limited to the injected area. Rabbits that had been given three weekly intravenous injections of paratyphoid vaccine were used by van der Slikke and Keuning.[186] A single injection of 10 mg of ACTH was given to one group nine days later and to a second group six months later. The first twenty-four hours after the administration of ACTH, agglutination titers showed a tendency to fall. A third group of animals was given ACTH twenty days after the last antigen administration and the animals were sacrificed after twenty-four hours. Spleens of rabbits so treated produced about twice as many antibodies as the controls. Appel and co-workers[2] gave patients an intradermal injection of 0.2 cc of a suspension of hydrocortisone acetate containing 25 mg per cubic centimeter. This was followed by an injection of the antigen in the same site. A control was given the antigen without hydrocortisone. Hydrocortisone produced total inhibition of the tuberculin reaction in six of ten patients, partial inhibition in two and no inhibition in two. The Frei test was inhibited in four and partially inhibited in one. Similar results were obtained with the other antigens. Microscopic studies showed that hydrocortisone produces atrophy of the epidermis and suppresses the formation of the histologic infiltrate so characteristic of these delayed reactions. Clinical experience indicates that the concomitant use of corticotropin or cortisone does not interfere with the "hyposensitizing" process with specific pollen or other allergens.[132] While the experience with tetanus toxoid and other immunizing injections under the influence of this hormone is not as great, the general opinion is that it does not interfere with immune processes with these antigens.

Rose[148] reviewed and summarized the relationships between histamines, hormones and hypersensitivity. He noted that although the role of histamine is characteristic of the acute anaphylactic state in animals, this agent can be demonstrated with certainty only in human subjects who show hypersensitivity to cold. The actions of the corticotropic hormones on various allergic states were reviewed. The author also summarized experimental evidence which indicates that there is some relationship between histamine, metabolism and adrenocortical activity.

Gianotti[65] determined the histamine blood level of a patient with herpes gestationis by the method of Code and found that it was about 180 times normal. The histamine level in the blood of the patient with dermatitis herpetiformis was also markedly increased. With ACTH administration it was found that the histamine blood level fell and this fall was independent of

the decrease of circulating eosinophils. The blood histamine level seems to be influenced by ACTH administration only if it is higher than normal. It had previously been shown that the urinary excretion of histamine was increased in allergic patients treated with ACTH soon after its administration, although significant modification of blood histamine levels was not noted.

Kerby and Barrett[86] have been interested in the relationship of adrenocorticosteroid hormones to the process of infection, inflammation and repair. Previous work had shown that there is an inhibition of the development of granulomatous barriers between irritants and tissues affected by the steroid hormones. Opinions vary, however, as to how alterations in responsive tissues are induced. Effects on vascular elements as well as direct metabolic effects upon leukocytes and connective tissue elements involved in the reaction have been studied. Observations have indicated that increased capillary permeability is prevented, arteriolar tone is slightly increased, damage to the endothelium of arterioles and venules is prevented, and growth of capillary loops is delayed in experimental animals. These are vascular effects possibly contributing to the decreased cellular response at the site of injury. Opinions differ as to inhibition of fibroblastic growth by cortisone in experimental chick embryonic tissue cultures and other animals. The authors undertook to determine whether a direct cellular alteration is demonstrable in man during ACTH or cortisone therapy, and whether the change persists when the tissue is removed from homeostatic influences to an environment *in vitro*. Leukocytes were studied because these cells are readily and repeatedly available and they play a role in the general response of the body to injury. As an index to cellular injury, the release of an enzyme (lysozyme) from the cell was quantitated by measuring the amount of lysozyme appearing in the suspending medium under test conditions. The effect of ACTH and cortisone upon the response of leukocytes to injury was determined. Using leukocytes from steroid-treated and untreated human subjects and exposing these cells *in vitro* to hydrocortisone and Piromen® or hydrocortisone and mechanical trauma, it was found that significant alterations in response to injury was demonstrated by the leukocytes. The leukocytes under steroid therapy showed resistance to injury. The same lessened susceptibility to injury can be induced in leukocytes of patients who have received no hormonal therapy by exposing the cells to cortisone or hydrocortisone *in vitro*. The maximal protective effect of the hormones does not correlate with disappearance of the eosinophils and usually required several days for development. The *in vitro* effect of protection was apparent in five or six hours, in contrast to a period of several days necessary for the development of a similar effect *in vivo*.

It is known that circulating eosinophils are reduced regularly following the oral administration or injection of cortisone and hydrocortisone. This index was employed by Smith[174] as a measure of absorption or nonabsorption of the topical application of hydrocortisone ointment. Six grams of an ointment containing a total of 150 mg of hydrocortisone acetate was applied to the normal skin of eight volunteers without skin disease and into the affected area of seven patients with eczematous dermatoses. A control circulating eosinophil count was done the day before the applications and circulating eosinophil counts were repeated four, six and twenty-eight hours after inunction. The control group was treated in a similar fashion. The studies revealed no consistent alteration in the counts either in the

normal volunteers or in the hospitalized patients with generalized skin disease. These studies indicate that there was not sufficient absorption to produce a drop in circulating eosinophil count, and show the absence of systemic effect of locally applied hydrocortisone in this experiment.

Long[96] used the response to intradermal tuberculin as a measure of allergic hypersensitivity in albino guinea pigs injected with BCG. Cortisone depresses sensitivity to tuberculin in the guinea pig, and it is thought that cortisone interferes with anabolism of glutathione in the course of a general interference with protein synthesis. In the guinea pig diet it was found that the action of cabbage in antagonizing desensitization by ascorbic acid is almost certainly due to sulfur-containing amino acids, probably methionine; cortisone antagonizes this effect. It was suggested by Moll and Hawn[111] that in rabbits ACTH interfered with the production of lesions by alteration of tissue reactivity. Cortisone influenced the picture by the inhibition of antibody formation. Bujard et al[16] studied the effects of cortisone applied topically or by injection on the production of mitoses in the skin of the nipple of guinea pigs. The results showed that cortisone does not influence mitotic growth stimulated by certain agents which include hormones. It does, however, exert a diminishing effect on mitoses stimulated by dinitrochlorbenzene applied to the nipple of nonsensitized animals.

Benjamin and Cornbleet[10] compared the effects of pain-producing substances when injected alone with the sensations produced when the substance was injected with an analgesic agent intradermally. Pain-producing agents used were thiamine hydrochloride, crude liver extract and histamine phosphate. The relative analgesic effects of the following substances were determined: cortisone acetate, 25 mg per cubic centimeter, hydrocortisone acetate in the same dose; suspension media for these two agents; Chlor-trimeton and procaine hydrochloride, 1 per cent. Immediate analgesic effects were noted with the use of the hormones, cortisone and hydrocortisone. Delayed effects, however, were not as well controlled by these agents as with procaine hydrochloride. The findings indicate that the mechanism of the analgesic action of the hormones studied is probably different from that of antihistaminics and local anesthetics. These agents presumably play a role in some of the chemical intermediates which then act directly on the terminal nerve endings.

Topical Use of Corticosteroids—Malkinson and Wells[102] treated seventy-one patients who had chronic eczematous dermatitis and atopic dermatitis using hydrocortisone ointment locally. Paired comparison tests as well as the ointment base alone were used as controls. The authors stressed the individual response to this agent; the rapid recurrence on cessation of treatment and the lack of response in psoriasis, pemphigus, discoid lupus erythematous and generalized exfoliative dermatitis. Hydrocortisone ointment had no effect on the development of erythema from ultraviolet light. Friedlaender and Friedlaender[55] studied 159 patients with atopic dermatitis, eczematous contact type dermatitis, chronic eczema of the hands, lichen simplex chronicus and otitis externa. They used 1 and 2.5 per cent hydrocortisone ointment. The free alcohol of hydrocortisone as well as hydrocortisone acetate appeared to be clinically effective and about equal in effectiveness. Improvement continued as long as the preparations were applied and relapses occurred within two or three days, in most cases. The authors made an attempt to classify the lesions which responded more

favorably and felt that excoriated, papulovesicular, scaling and lichenified lesions did best with these preparations. Urticarial and deep vesicular lesions responded least favorably. It was found best to begin patients with the 2.5 per cent concentration of hydrocortisone and when improvement appeared, it could be maintained with the 1 per cent concentration. The addition of 0.5 per cent neomycin to the hydrocortisone preparations was particularly effective in eruptions in which impetigo occurred secondarily and in patients with otitis externa. In nine patients the condition was aggravated, probably by the ointment base. It is emphasized that these preparations are for the symptomatic control of eczematous allergic dermatoses only. Further allergic studies should not be neglected in the management of these problems. A group of patients with atopic dermatitis, circumscribed neurodermatitis, anogenital eczema and allergic eczema were treated with various strengths of hydrocortisone ointment by Heilesen et al.[77] Favorable response to this preparation was noted in most patients treated with the above conditions. The authors noted that in patients with atopic dermatitis and seborrheic dermatitis, impetigo may suddenly develop during an otherwise successful course of therapy. It was thought that the immediate results of the use of this preparation were very promising. Hydrocortisone ointment used locally had no effect in lupus erythematosus, pemphigus vulgaris, psoriasis, pustular bacterids, and lichen planus.

Hydrocortisone ointment was used by Witten et al[192] in the treatment of thirty patients with infantile eczema, employing simultaneous paired comparison tests with 2.5 per cent hydrocortisone-free alcohol ointment on one side, and the vehicle (wool fat, 15 per cent, liquid petrolatum, 10 per cent, and white petrolatum, 75 per cent) was used on the other. All infants had atopic dermatitis in all stages of the disease. A beneficial effect was noted in 67 per cent of the patients and the control preparation did not improve the affected area as readily as did the active medications. Intolerance to the preparations was not seen and no undesirable systemic effects were noted, even though in nine infants approximately half of the body surface was rubbed with hydrocortisone-free alcohol ointment two or three times a day. A group of 104 children ranging between the ages of one month and ten years, who had infantile eczema, were treated topically by McCorriston[107] over an eight-month period with hydrocortisone ointment. The preparation was used in various concentrations and in various bases. Paired comparison tests were used in some patients. The usual effect noted by mothers was that of diminution of pruritus and weeping, softening and clearing of lichenified lesions. This occurred, as a rule, within twenty-four to forty-eight hours. The hydrocortisone ointment in every case produced a better effect than the control or the base used alone. In this series most of the children showed 75 to 100 per cent improvement and this was maintained in 60 per cent of the patients after therapy was discontinued. Studies on possible systemic effect using the 17-ketosteroids or corticoid excretion revealed no evidence of systemic effect or of absorption. No allergic sensitization to the ointment was noted. Robinson and Robinson[147] treated 418 patients with hydrocortisone acetate and hydrocortisone-free alcohol in a lotion base, in a greasy ointment base and in several greaseless bases. These authors found the same results as reported by Witten et al and McCorriston. Of the 172 patients with atopic dermatitis, 144 were relieved. Forty-nine of seventy-one patients with contact dermatitis, and fifteen of seventeen

patients with stasis dermatitis improved with treatment. Prompt relief was seen in pruritus ani and pruritus vulvae in forty-five patients. Five patients were not relieved.

Fromer[60] discussed dermatologic concepts and management of pruritus ani. The topical application of the corticosteroids has been highly effective in the symptomatic control of itching in pruritus ani. The preparation, when effective, may be discontinued gradually in order to avoid the "rebound" or recurrence seen with sudden withdrawal of the preparation. If the patient is not relieved appreciably in forty-eight hours with topical steroid therapy, it is usually necessary to change to another brand or form of the steroid hormone. Combinations of the corticosteroids with antibiotics, tars, sulfur and other commonly used dermatologic modalities are in clinical research.

Previous reports have indicated that oral cortisone given over a four- to seven-day period was effective in the management of Rhus dermatitis. Eskind et al[45] employed topical hydrocortisone in evaluating seventy-nine cases of Rhus dermatitis. The patients were ambulatory. The agents used were hydrocortisone lotion (0.2 per cent), hydrocortisone ointment (1 per cent and 2.5 per cent), and hydrocortisone cream (2.5 per cent). In addition, placebos in the form of lotion and ointment were also employed. The results indicated that the active preparations were not effective in the ordinary course of Rhus dermatitis. In four patients, however, who presented a massive angioneurotic edema as the original symptom, the preparations produced an excellent response. Goldman and Preston[68] studied forty-seven patients with varying degrees of poison ivy dermatitis. In their previous experience, they had reported that corticosteroids were effective agents if given over a brief period of time for the severe, uncomfortable episodes in poison ivy dermatitis. In this group, however, they used hydrocortisone and found that, given orally, the preparation is, dosage for dosage, more effective than cortisone. In addition to oral therapy, an ointment containing 2.5 per cent hydrocortisone in a lanolin base was found to be effective.

Baer and Litt[6] discussed otitis externa and noted that it is usually a manifestation in the ear canal of such common dermatoses as seborrheic dermatitis, psoriasis, eczematous dermatitis and atopic dermatitis. Microorganisms may appear as secondary invaders. The most important and commonest finding is *Pseudomonas aeruginosa.* As a rule, dermatologists avoid greasy preparations in the external canal. Ten patients with otitis externa were treated with hydrocortisone or a combined hydrocortisone antibiotic suspension in aqueous form. The patients were asked to use three drops of the suspension in each ear canal twice daily, without subsequent insertion of an absorbent cotton tampon. Re-examination after four to seven days revealed in most instances that the erythema and exudation in the ear canal had subsided and the canal had become much drier. It is emphasized that this is a preliminary report. A more extensive trial is suggested because of the good results in this small series.

Systemic Use of Corticotropins and Steroid Hormones—A general description of fibrinoid degeneration of collagen and the group of so-called collagen diseases is given by Marañon and Gimena.[103] They treated two patients in advanced stages of scleroderma with sclerodactylia with corticotropin and later cortisone and noted improvement in both patients. Although the authors were encouraged with these preliminary reports, the

follow-up period was short. Pike and Elder[126] reported a thirty-six-year-old white woman with typical lesions of erythema nodosum. An attack of erythema nodosum was easily controlled with oral cortisone, but she had three or four subsequent attacks as soon as the drug was discontinued. After the fourth relapse of erythema nodosum, she was given a maintenance dose of cortisone. A total of 3,325 mg of cortisone was required and no further relapses were noted. The authors suggested that the sedimentation rate is the best index for the control of erythema nodosum. Fyles and Rose[61] administered ACTH gel subcutaneously to a number of patients with respiratory allergy as well as to individual patients with pemphigus, periateritis nodosa and penicillin sensitivity. The average length of treatment was thirty days and the longest 239 days. The doses ranged from 10 to 80 units per injection, which were administered at intervals of from one to seven days. The patients with skin lesions started to respond within forty-eight hours of therapy. Eosinophil counts showed about a 50 per cent drop in the first twenty-four hours after therapy was started. Mild urticaria was the only side effect noted during the treatment of four patients. In acute idiopathic thrombocytopenic purpura, corticotropin or cortisone has a favorable action on the course of the disorder according to Pariser and Wasserman.[123] The drugs suppress the causes of humoral or vascular factors while the patient is under hormone therapy. Because relapses are common, the hormones should be continued for three to five months after therapy is instituted. In chronic idiopathic thrombocytopenic purpura, the hormones may be used until splenectomy is undertaken. The use of the hormones did not interfere with wound healing in any of the patients studied who were subjected to splenectomy.

Occasionally, it is necessary to administer corticotropins to a patient who is pregnant. Katzenstein and Morris[84] presented a case report of a thirty-six-year-old woman who suffered with dermatitis herpetiformis of pregnancy. She was treated with ACTH and cortisone during the major portion of her pregnancy, with good control of dermatitis. The birth of a normal baby ensued. Seven other cases of normal births after therapy with steroid hormones during pregnancy are reviewed.

Davis[35] reported five cases of penicillin hypersensitivity; two patients had urticaria, two diffuse erythema, and one patient erythema multiforme-like eruptions. The patients had been given antihistaminics, ephedrine, epinephrine, and calcium gluconate without effect. An intramuscular injection of 50 mg of cortisone was given to each patient and there was good symptomatic response in from five to eight hours. Additional treatment using the same dose was adequate for recurrences. Shulman et al[169] treated twenty-four patients who showed reactions to various drugs, thirteen of whom had reactions caused by penicillin, eight by horse serum, and one each by sulfonamides, para-aminosalicylic acid and gold salts. The reactions were urticarial in nature and seven patients had arthritic symptoms. Previous treatment had consisted of epinephrine, antihistaminics and intravenous procaine which had not entirely controlled symptoms. The patients therefore were treated with ACTH, intravenously or intramuscularly, or with oral cortisone. The average total dose of cortisone was 760 mg. The length of treatment varied from two to seven days. Patients showed improvement within forty-eight hours when they were given either cortisone or ACTH and some began to show relief from annoying itching within a few hours after treatment was instituted. Of 600 patients who had been given ACTH in Johns Hopkins Hospital over the past

three years, five had reactions to the drug. The more severe reactions occurred after the use of beef ACTH. It is the opinion that oral cortisone is probably the simplest, most effective and least expensive method of treating severe drug reactions.

Limitations and Untoward Effects—O'Leary[120] stated that cortisone and corticotropin will not cure patients with diseases of the skin. These agents may extend the life expectancy of those who have acute systemic lupus erythematosus, or other collagen disease, and pemphigus. In the inflammatory dermatoses, such as urticaria, dermatitis venenata, drug eruptions and erythema multiforme, the steroids will shorten the course of these disorders. It is important to note that in psoriasis, seborrheic dermatitis, dermatomyositis and neurodermatitis, temporary improvement will occur but when the drugs are discontinued, relapses are more severe than the original condition. Complications of steroid therapy are discussed.

After a study of almost forty years, Sulzberger and Witten[179] reported the results of treatment of thirty-five patients with severe, serious and sometimes fatal dermatoses. Patients required from 300 to 1000 mg of cortisone daily, and the dose was rapidly reduced to the lowest effective dose which prevented new crops of lesions. The maintenance dose was extremely variable in most patients; it ranged from 5 mg every second or third day to as much as 100 mg of cortisone daily. Recurrent episodes were checked by raising the cortisone level to that dose which suppressed symptoms. The patients were on a salt-poor diet and given 3 gm of potassium chloride daily. Blood pressure and weight were recorded daily and the patients were watched for mental changes. Blood pressure readings were recorded weekly and urinalysis was done as required. It was thought that in such collagen diseases as acute disseminated lupus erythematosus, the dosage of cortisone was maintained to suppress symptoms in spite of physiologic effects such as weight gain, moon facies, peripheral edema, chemical changes in the blood and even mild psychic disturbances. In this connection an editorial appeared in *The Journal of Allergy* on the delayed effect of long-continued administration of therapeutic doses of corticosteroids. The early hormonal side effects of salt, water and sugar metabolism are widely known and easily detected, and are reversible except in patients with serious complicating diseases. Mental effects, which are occasionally noted, are sometimes more serious, but they also tend to be reversible, and spontaneous recovery is the usual finding. The activation of unsuspected late tuberculosis and of peptic ulcer will often prove more difficult and dangerous problems than the disease for which the corticotropin was prescribed. The problem of the masking of infections is noted. Decalcification of the skeleton to the point where collapse of vertebral bodies and pathologic fractures occur is a vexing problem in long-continued corticotropin therapy. The editorial[41] quotes the work of Bennet and others who found that the adrenal glands of persons who have received cortisone for more than five days in total doses of more than 450 mg show definite changes which may persist for as long as four to six weeks after treatment has been discontinued. The anatomic changes seen in the adrenal cortex indicate that the gland would be unable to function during the periods of stress. A number of instances of postoperative deaths, apparently due to acute adrenal cortical insufficiency in patients who have previously received cortisone therapy, are described as instances of this situation. In periods of stress, including accidents and surgical

operations, it becomes necessary to support the adrenal glands in patients who have previously been given cortisone therapy.

Dougherty, Reisch and Lewis[39] reported six patients with widespread dermatoses complicated by staphylococcic bacteremia during the administration of cortisone or corticotropin. In one patient who died, an autopsy showed bronchopneumonia due to hemolytic Staphylococcus aureus, multiple scattered abscesses and acute glomerulonephritis. It seemed that the number of cases of bacteremia was disproportionately high when compared with similar cases in which the steroids were not given. This series of cases emphasizes the potentially dangerous complications which occur with the administration of corticotropin and cortisone. The authors stressed the fact that these hormones should not be used indiscriminately and that the patient should be watched carefully during their administration. The reviewer had a similar experience when ACTH was first available. A fifteen-year-old girl with a widespread exfoliative dermatitis was given ACTH in 15 to 20 mg doses daily by slow intravenous infusion. All the usual precautions were taken and she had been afebrile during the entire course of the exfoliative dermatitis. On the sixth hospital day she suddenly became febrile with a temperature of 104° and remained in this state for seven or eight days in spite of all investigative studies, supportive and antibiotic therapy to determine the source of the fever. Autopsy showed a terminal bronchopneumonia and multiple scattered abscesses including one abscess, measuring 1 cm, in the myocardium.

Swift[182] reported the case of a thirty-five-year-old woman who had received ACTH for about one year. The doses had been given intermittently as required. She was given an injection of ACTH for an asthmatic attack. About one hour after the injection, giant urticaria, nausea, diarrhea, and severe dyspnea developed. The reaction gradually subsided following symptomatic treatment. This patient showed positive skin test reactions to aqueous pork and beef ACTH as well as pork ACTH gel. Routine allergy extracts containing these antigens gave negative reactions.

An immediate anaphylactoid reaction to porcine corticotropin (ACTH) which was fatal was reported by Hill and Swinburn.[78] A reaction after a long course of porcine corticotropin nine months earlier was undoubtedly due to anaphylaxis. Neither previous history nor direct scratch skin tests in the patient elicited hypersensitivity to pork or beef. Death was the result of prolonged cerebral anoxia and associated circulatory collapse of twenty-five minutes duration. There were no clinical signs of urticaria, angioedema or bronchospasm before or during the anaphylactoid reaction. Autopsy findings indicated that death was caused by anaphylactoid shock.

MISCELLANEOUS ALLERGIES

Long[97] presented a comprehensive review of the pathogenesis of rheumatic fever and described the evidence in man of the role of bacteria in this disorder. It is suggested that hemolytic streptococci cause rheumatic fever and that streptococcal allergens and toxins act synergistically upon mesenchymal cells to produce a rheumatic syndrome in susceptible persons, and that the response to streptococcal allergens is of the type seen with tuberculin and not of that seen in anaphylaxis. The hypothesis is advanced that susceptibility of rheumatic fever and the sensitivity to bacterial allergens amount to the same thing. The rheumatic fever patient and the BCG-infected guinea pig are alike in showing bacterial allergy of the tuberculin type, in their inability to synthesize ascorbic acid, in their response to cortisone, and in the fact that their susceptibility is de-

creased by diabetogenic agents and increased by antidiabetogenic agents, by hyperthyroidism and by hypothyroidism. It is suggested that cortisone impairs SH synthesis in the skin of the guinea pig, thus facilitating the oxidation of ascorbic acid to dehydro-ascorbic acid, which increases the local concentration of glucose-1-phosphate, leading to desensitization. It is unlikely that cortisone exerts this antiallergic activity by inducing qualitative or quantitative changes in the antibody or by interfering with the union of antibody and allergen.

Doub et al[38] studied fifteen male and four female patients between the ages of two and one-half and sixty-four years, with polyarteritis nodosa, between 1943 and 1952. Eleven patients have died and postmortem examinations were done in nine. Seven of the eight remaining patients are living and without symptoms. Analysis of x-ray changes in six patients with evidence of pulmonary involvement disclosed the presence of parenchymatous infiltration in all. In two, the familiar bat-wing areas of infiltration were demonstrated. These findings are not specific but may be suggestive. Major pulmonary symptoms of parenchymal roentgenologic abnormalities indicate a poor prognosis. Lyell and Church[99] reported on the cutaneous manifestations of polyarteritis nodosa. It has been estimated that 25 per cent of all patients have cutaneous changes which help to establish the diagnosis. The acute stage is accompanied by polymorphic exanthemas. Livedo and ulceration occur in the chronic stage. Nodules, being the essential lesion, may occur at any stage. They occur in crops, have a tendency to grouping and may localize over the course of an artery. They may regress quickly or persist for months. They may be painful, or changes may occur over the skin leading to ulceration. Multiple subcutaneous hemorrhage may occur due to rupture of vessels. Gangrene of the extremities may be seen and Raynaud's phenomenon has been described. Purpura is the commonest finding of the acute stage of polyarteritis nodosa. This is accompanied by urticaria and erythema multiforme-like lesions leading to the polymorphism seen in the acute stage. Livedo reticularis is not an uncommon response to cold in the chronic form of the disease. Three cases are presented. The authors concluded that the visceral form of the disease, in which the skin is involved inconstantly, is more serious and often fatal.

Palitz[122] believed that the concept of the "collagen diseases" introduced by Klemperer, Pollack and Baehr has been of great value in furthering our knowledge of the group of diseases which include periarteritis nodosa, disseminated lupus erythematosus, scleroderma and dermatomyositis. It has been revealed that connective tissue, far from being an inert and unimportant mechanical cement substance, is a dynamic, labile and important element of the body structure subject to control and maintenance by hormones, enzymes, vitamins and other unknown factors. Fibrinoid degeneration, at least in disseminated lupus erythematosus, is now believed to be due to breakdown products of desoxyribose nucleic acid. The depolymerization of this substance possibly is controlled directly or indirectly by the lupus erythematosus serum factor of Haserick and Hargraves. Because recurrent edema and a polymorphic skin eruption may be one of the first signs of dermatomyositis in childhood, it is of interest to study the cutaneous features of this serious disease. Roberts and Brunsting[145] reported that recurrent edema involving the face and extremities is seen early in its course. This may involve the eyelids alone in association with a faint heliotrope hue and tiny telangiectasia. Erythematous suffu-

sion gradually extends over the cheeks, the entire face, neck and shoulders. Sometimes the eruption becomes widespread; in one child it had characteristics of exfoliative dermatitis. In addition, small, scaly, bluish-red plaques may be present over the bony protuberances of the knuckles, elbows, knees and ankles. These may persist or disappear, with superficial atrophy remaining. Urticaria occurred in two children; in one child it preceded the onset of other symptoms of dermatomyositis by several months and presented a diagnostic problem in itself.

Kass et al[88] reported that the coexistence of sarcoidosis with periarteritis and panarteritis suggests that its pathogenesis may be the same as that of various collagen diseases. Three case reports are published which support this thesis. They believe that the symptom of erythema nodosum could be defined as a hypersensitivity disease with a plurality of causes. It follows certain criteria of allergic phenomena. Furthermore, the response of some cases of sarcoidosis to cortisone would lend further support to the hypersensitivity theory. Both sarcoidosis and hypersensitivity display a similar morphologic reaction to stress.

The Shwartzman phenomenon [155] as well as the Arthus reaction, and its relationship to clinical medicine is briefly reviewed in the *Lancet*. Quotations are taken from Rostenberg's current review. The Shwartzman reaction may play a part in some of the infective purpuras and hemorrhagic forms of the common fevers. Possibly infective emboli prepare the skin sites and the reaction is elicited by circulating toxins, or alternatively, the toxins may be the preparatory element. This may also happen in tuberculides, the bullous and necrotic form of leprosy, and the so-called "butcher's pemphigus." Various gangrenous skin lesions have been described in association with chronic inflammation of internal organs, notably ulcerative colitis. The lesions of ulcerative colitis have been reproduced experimentally by the Shwartzman technique; and ulcerative colitis may in turn furnish the infective focus that leads to the production of lesions in the skin by the same mechanism. A case of ulcerative colitis with gangrenous skin lesions apparently responded strikingly to a hyperimmune streptococcal serum, according to Schmidt (1953).

Patients with various types of lymphoblastoma, including Hodgkin's disease, mycosis fungoides and the various leukemias, were tested by Rostenberg and Bluefarb[153] for both the immediate and delayed types of reaction to tuberculin, trichophytin, oidiomycin and histoplasmin. These patients were also studied by the use of an obligatory whealing agent, such as histamine and other agents. The authors found pronounced depression of the delayed type of allergic reactivity, but less information was obtained from the immediate type of allergic reactivity. This unusual depression of tuberculin type reactivity was thought to be an enzymatic adaptation to the antigen. It is possible that the primitive reticulum cell loses this enzymatic adaptation in these proliferative processes. It is thought that the lack of tuberculin reactivity in sarcoidosis may be based on the same mechanism. Schier[158] used five antigens in addition to histamine for intradermal injections in 114 patients, of whom thirty-three had Hodgkin's disease. The remainder were controls. The antigens included mumps, *Candida albicans, Trichophyton gypseum* and purified protein derivative of tuberculin. A striking cutaneous anergy was noted in patients with Hodgkin's disease. The reaction to histamine, however, was normal. If this lack of response is confirmed in a large percentage of patients with Hodgkin's disease, this form of investigation may help in

the diagnosis of questionable cases of this disease. One patient with reticulum cell sarcoma was completely unreactive to the antigens. This is interesting in view of the current opinion that Hodgkin's disease probably arises from the reticulum cells. The reviewer has noted that in some patients with mycosis fungoides, the response to tuberculin is unchanged from the normal response. Studies are under way to see whether anergy develops in these patients when the mycosis fungoides becomes terminal and there is evidence that reticulum cell sarcoma has developed. In a study of antibody formation in patients with malignant lymphomas, Geller[63] tested twenty-four patients with either lymphosarcoma or Hodgkin's disease, and sixteen normal individuals. The patients received 0.1 mg of specific pneumococcal capsular polysaccharide I (S-1) subcutaneously. Two to six weeks later, antibody titers to S-1 were made on the blood of all subjects. The results confirmed the concept of the poverty of antibody response in patients with malignant lymphoma.

A white boy, age eight, was presented by Burgoon and Scott,[17] with depigmented areas on the buttocks and small papules on the arm which appeared in July, 1953. Additional papules (nodules) occurred later on the arms, legs and trunk and some broke down to form ulcerations. A biopsy of the lesions was reported as malignant histiocytoma; mycosis fungoides: lymphoblastoma. In discussion, the reviewer who saw this boy in Boston, found that the lesions had occurred on the exposed areas in the summertime when the boy was at a summer camp. There was a history of repeated insect bites. Both the parents were allergic and were marked reactors to insect bites. On further studies of the microscopic pictures, the reviewer made the diagnosis of insect bite granuloma in this patient who was himself allergic and had a highly allergic family history. This case again emphasizes the importance of investigating the allergic background and properties of patients with questionable lymphoma, since the microscopic picture of insect bite granulomas in an allergic individual may simulate lymphomatous disease. Two years after this presentation the boy still had no clinical evidence of lymphoma.

Immunization of newborn infants was described in 1951 by Hesselvik and Vahlquist[133] of Sweden. They practice vaccinating the infants with BCG at birth, but do not begin the triple antigens until the infants are three months of age. Di Sant' Agnese revived interest in this subject a few years ago with several publications, one of which is entitled "Simultaneous Immunization of Newborn Infants Against Diphtheria, Tetanus and Pertussis: Production of Antibodies and Duration of Antibody Levels in an Eastern Metropolitan Area." More recently (1954), Dancis and Kunz have reported "Studies of the Immunology of the Newborn Infant." Extremely few pediatricians probably would recommend instituting active immunization on the first day of life.

Stark et al[175] over many years have studied more than 300 patients with recurrent aphthae. The point is made that recurrent aphthae are usually solitary lesions, although there may be successive lesions in new locations before the older lesions have healed. Lesions of primary herpes are usually multiple. Use of elimination diets, skin tests and antihistaminics have no consistent effects on the frequency of recurrences. Repeated smallpox vaccinations were tried in 50 cases, with no consistent effects. It was not possible to demonstrate specific herpetic intranuclear inclusions in lesion biopsies in twenty-three cases. Using sera of sixty-two subjects for examination of antibodies against herpes simplex by means of complement

fixation or virus neutralization techniques, or both, the authors concluded that their findings by this method make a herpetic etiology of this disorder unlikely. The viral cause of aphthous ulcers has not been proved according to a notation in the *Journal of the American Medical Association*[138] in 1954. Several careful studies have failed to determine that it is caused by the virus of herpes simplex. The herpes simplex virus cannot be isolated from the lesions, and the biopsy findings are not characteristic. Although the precipitating causes of recurrent aphthous ulcers are numerous, it is rare that any specific exciting agent can be proved in the individual case. Skin tests to determine the possible sensitivities to foods are useless. Other factors that sometimes seem responsible, although difficult to prove definitely, are nervous tension and fatigue. There is no proof that repeated vaccination is of any value. It is possible that a short course of cortisone or corticotropin therapy administered promptly at the onset of the symptoms of developing lesions might be helpful.

A twenty-four-year-old sailor was reported by Tolman and Fox[183] who developed three slightly tender, indurated, red, deep seated plaques on the anterior surface of the thighs. The first lesion subsided spontaneously in three weeks. The second broke down, draining watery material, and healed spontaneously. The biopsy presented characteristics of nodular nonsuppurative panniculitis (Weber-Christian disease). The reviewer, in a discussion of this case, stated that he had seen a patient in the last year of military service (1945) who presented this type of lesion in whom the lesion could be reproduced by the local application of cold. If an ice cube were applied to an exposed area, the reaction within twenty-four to thirty-six hours consisted of an indurated erythematous plaque which became very firm and was followed by ulceration at the site. It healed with minimal scarring. The pathologic picture was reported to be consistent with Weber-Christian disease. This patient had urticaria clinically when exposed to cold.

Ferris et al[50] added 25 mg of Pyribenzamine to transfusion blood. A total of 607 blood transfusions was reported. In this group there was one allergic reaction, one hemolytic reaction and no pyrogenic reactions. In a control series of 742 transfusions in which Pyribenzamine was not used, there were twenty-one allergic reactions and thirty-two pyrogenic reactions. The authors speculated that the reactions were probably due to liberation of histamine. Hall and Di Raimondo[74] reported a forty-four-year-old married woman who developed pyrexia, chills and urticaria following intravenous administration of concentrated salt-poor albumin. The antigen was considered a denatured protein, and desensitization by the intracutaneous, subcutaneous and finally by intravenous routes was successful.

The intolerable itching associated with chronic obstructive jaundice is very difficult to manage.[130] Good results have been reported from treatment with procaine amide (Pronestyl®) hydrochloride, ergotamine, and androgenic substances given to the point of physiologic reactions. Too often, however, the results are found wanting. Topical applications are generally useless. According to Lundy in "Clinical Anesthesia" (1942), procaine given intravenously has afforded temporary relief.

Woodburne et al[194] reported their experiences in four cases of solar dermatitis of various types which responded to the administration of quinacrine. They have also used this preparation in four cases of hydroa aestivale, six cases of solar urticaria, and several of the polymorphic and

prurigo types of solar dermatitis. All patients responded. Patients are given 0.1 gm of quinacrine hydrochloride once a day for a week, then twice a day for a week, and finally three times a day for a week. The progression is then reversed. Some patients get along on 0.05 gm daily or every other day without flare-ups. Porter[128] studied a woman, age thirty, who complained of irritation from sunlight "all her life." By means of special filters, the author determined that his patient was sensitive to active wave lengths extending from the ultraviolet region throughout the visible spectrum into the infrared. Such a wide range of sensitivity is unusual. It has been suggested that certain abnormal compounds are present in the skin of these patients which are altered by the action of light, and that such changes lead to the formation of H-substance and whealing. These intermediary substances are difficult to identify. According to the allergic theory, sensitization of certain cells on subsequent exposure leads to release of H-substance and whealing. Many patients with urticaria solaris demonstrate other manifestations of allergy, with tissue and blood eosinophilia. Passive transfer has been successfully accomplished in some cases due to wave lengths shorter than mμ 370. Patients are relieved by antihistamines. A successful preventive cream contained titanium oxide 5 per cent, quinine bisulfate 5 per cent, para-aminobenzoic acid 2 per cent, menthyl salicylate 10 per cent, and water soluble base to 100. Chloroquine sulfate, 150 mg twice daily, was also effective.

Acute and chronic reactions to black fly bites were studied by Gudgel and Grauer.[71] This fly produces a variable type of reaction in the host. The normal reaction is a small ecchymosis with a blood crust followed in several hours by a small pruritic papule which persists for a few days and disappears without residuum. Some persons show erythema and wheals. Occasionally, the tenderness and appearance are similar to those of a bruise and, less commonly, a severe, acute reaction is seen with constitutional symptoms. Persistent lesions, however, were observed in nine patients in whom the duration was six to eleven months and the lesions were indistinguishable from nummular eczema. Hard, pigmented, rough, pruritic nodules were also present in some patients. The type of reaction to repeated fly bites was influenced to some degree by the allergic tendency of the patient. Desensitization to wasp sting may be accomplished by an antigen which uses the body of the insect minus the poison sac, according to a note in the *Journal of the American Medical Association*.[135] It has been shown that a susceptible person is allergic to any portion of the wasp and not specifically to the venom. The usual rules for desensitization, such as those followed with routine pollen extracts, apply to desensitization with insect antigens. The patient should be able to tolerate the most concentrated preparation before he can be considered to be immune. The reviewer instructs such insect-susceptible patients to use epinephrine in an ampule-needle combination called Ampins®, and containing epinephrine. An injection can be given immediately by removing a plastic covering over the sterile needle. This item, so far as is known, has been removed from the market. I have written the company concerning its usefulness but apparently there has not been sufficient demand for it by allergists. A patient who has previously developed edema of the glottis and generalized urticaria from a bee sting is in serious danger of a severe reaction from the next sting, possibly even death before any medical aid can be obtained.[140] No one knows the duration of desensitization, although patients who have been treated against the Hymenoptera order in most instances

may retain immunity over a period of years without repeated courses of treatment. After treatment of some patients, clinical experience suggests that although bees always selected them previously, they no longer come near these patients. Other patients, after treatment, have experienced a bee sting that was a minor incident with little or no local reaction and no systemic effects. Good extracts for desensitization are difficult to obtain.

It has long been felt that there is a relationship between patients with papular urticaria and sensitivity to insect bite. Shaffer et al[163] reported that patients with papular urticaria have positive delayed tuberculin type skin reactions to the intradermal injection of the insect antigen. The authors studied a number of lesions of papular urticaria from the standpoint of histology and compared their findings with those of patients who showed positive urticaria on delayed skin reactions to mosquito, bedbug or flea antigens as well as the histology of ordinary insect bites. They concluded that the histologic findings support the concept that papular urticaria is often an allergic disease induced by the bites of insects.

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ATTENTION: AUTHORS

There has been a tendency lately for authors having manuscripts accepted for publication in the ANNALS OF ALLERGY to return the galley proof with little or no correction. In most instances, when proofs are returned marked "O.K. No Corrections," it throws the responsibility for correction on the Managing Editor's staff at the time page proofs are checked. Corrections at this time are more costly, delay publication, and are largely unnecessary. Hereafter, when a galley proof is returned to the publisher still needing numerous corrections, it will be sent back with the original manuscript to the author for proper correction, as this is entirely his responsibility. This may mean that publication of the paper will be delayed for one or more issues. Your cooperation will be greatly appreciated.

In Memoriam

MARTIN LUTHER HARSHMAN

It is with regret that we announce the death on October 19, 1955, of Dr. Martin Luther Harshman, 308 North Eighth Street, Lafayette, Indiana.

Dr. Harshman was born in Frankfort, Indiana, on August 19, 1913. He received his education at the Mulberry, Indiana, high school and Purdue and Indiana Universities, obtaining his B.S. degree in 1937 and his M.D. in 1939. His internship was taken at St. Vincent's Hospital, Indianapolis, in 1939 and 1940, and at St. Elizabeth's Hospital, Lafayette, in 1946. After deciding to specalize in otolaryngology, he took postgraduate work at Washington University, and was assistant ENT resident at Barnes Hospital in St. Louis. He also took short courses in bronchoesophagology at the University of Illinois, the anatomical and clinical course in otolaryngology at the Indiana University School of Medicine, and graduate instructional courses in allergy.

He was a member of the American Medical Association, Indiana State Medical Association and the Tippecanoe County Medical Society, and served on the staffs of St. Elizabeth's Hospital and the Lafayette Home Hospital, Lafayette, Indiana. He became an associate fellow of the American College of Allergists, June 13, 1949. At the time of his death he was affiliated with the Arnett Clinic in Lafayette.

Dr. Harshman was an ardent fisherman and was also interested in photography and the raising of tropical fish.

He is survived by his wife, Lucile, his mother, Mrs. Laura J. Harshman, a brother, Harold Harshman, and a sister, Mrs. Freda Rutan. To those who survive him, the officers and members of the College offer their sincere sympathy.

NICHOLAS K. EDRINGTON

Dr. Nicholas K. Edrington, who has been active in the affairs of the Southwest Allergy Forum, died suddenly on September 22, 1955. The officers of the College extend their sincere sympathy to his family.

CORRECTION

On Page 564 of the September-October issue of the ANNALS OF ALLERGY, in an article entitled "The Prophylaxis of Penicillin Reactions with Chlorprophenpyridamine Maleate Injection 100 Mg per Cubic Centimeter" by Donald B. Frankel and Robert E. Stutsman, the statement that Simon combined 3 mg chlorprophenpyridamine maleate (Chlor-Trimeton Maleate) in aqueous solution with 600,000 unit doses of penicillin and produced thereby a reaction rate of 0.4 per cent in 750 patients, should be corrected to read that Simon's penicillin was standardized at 100,000 units per ml and that 3 mg of Chlor-Trimeton was added to each ml and therefore 18 mg of the antihistamine was added to each 600,000 units of penicillin to obtain this reaction rate. This dosage is quite similar to that used by Frankel and Stutsman (20 mg per 600,000 units of penicillin).

News Items

NOTICE OF ELECTION OF OFFICERS AND REGENTS THE AMERICAN COLLEGE OF ALLERGISTS

Pursuant to Article V, Section 7 (g) of the By-Laws, the Nominating Committee has selected one candidate for each elective office, to be voted on at the next annual election. The selection which appears below is known as the:

OFFICIAL BALLOT

President-Elect ..... Orval Withers, M.D.
First Vice President ..... Merle Moore, M.D.
Second Vice President ..... Stephen Lockey, M.D.
Treasurer ..... John Gillaspie, M.D.
Secretary ..... Giles Koelsche, M.D.

Board of Regents—Three-Year Term
Sam Sanders, M.D.
Howard Rapaport, M.D.
W. C. Service, M.D.

"ARTICLE *Section 7 (g).—The Nomination of Officers.*—The Nominating Committee shall be composed of five (5) members: The President, two (2) members of the Board of Regents each of whom has served at least two (2) years on the Board, and two (2) past Presidents, both Regents and past Presidents to be selected by the Board. Not earlier than three (3) months, but not more than six (6) months after its selection the Nominating Committee shall pick one (1) candidate for each elective office and this shall be known as the official ballot. In making its selection it shall take into consideration the qualifications, fitness, capacity, standing and accomplishments in the field of allergy of those considered for selection, and all information contained in the membership records maintained in the Secretary's office as to any proposed selectees shall be seasonably supplied to the Committee for this purpose. The Nominating Committee shall report its selections to the Secretary-Treasurer's office and as soon as convenient thereafter, but not less than three (3) months before the ensuing election, notice of this official ballot shall be given to all voting Fellows of the College. This notice may be given either by publication thereof in the official organ of the College, ANNALS OF ALLERGY, or by mail. Additional nominations may also be made by petition, signed by ten (10) Fellows and sent to the office of the Secretary-Treasurer, provided said additional nominations are received in the office of the Secretary-Treasurer at least thirty (30) days prior to the next annual meeting. Nominations may also be made from the floor at any annual meeting. The election of officers and Regents shall be by ballot and shall be by a majority of the votes cast at the annual meeting."

The Nominating Committee
LAWRENCE J. HALPIN, M.D., *Chairman*
JOHN H. MITCHELL, M.D.
GILES KOELSCHE, M.D.
HARRY ROGERS, M.D.
MORRIS A. KAPLAN, M.D.

AMERICAN ACADEMY OF ALLERGY

The twelfth annual meeting of the American Academy of Allergy will be held in St. Louis, February 6-8, 1956, preceded by a Postgraduate Review on February 4-5. All meetings will be held at the Chase and Park Plaza Hotels.

BOOK REVIEWS

IDENTIFICATION OF ENTEROBACTERIACEAE. P. R. Edwards and W. H. Ewing. Offset, 179 pages. Minneapolis, Minn.: Burgess Publishing Company, 1955. Price, $4.00.

The essential theme of this monograph is the technique of isolation and identification of *Enterobacteriaceae* involved in human infection. The main emphasis, therefore, is on the genera *Salmonella* and *Shigella* (the latter including the Alkalescens-Dispar group). Special chapters are dedicated to the Arizona group, *Escherichia freundii*, the Providence and the *Klebsiella-Aerobacter* groups. A thorough and up-to-date account is given of the biochemical reactions and the methods of serologic identification of these organisms. Every page reflects the first-hand experience of the authors, who have devoted many years of work to this field. Uncertainties of nomenclature and classification are discussed with refreshing frankness.—A.J.W.

J.A.M.A. CLINICAL ABSTRACTS OF DIAGNOSIS AND TREATMENT. Edited by Noah D. Fabricant, M.D., Editorial Associate of the J.A.M.A. 636 pages, including index. New York: Intercontinental Medical Book Corp. with Grune and Stratton, Inc., 1955. Price, $5.50.

The Clinical Abstracts of The Journal of the American Medical Association are probably its widest read and most popular feature. The specialist reads them to make certain that he is abreast of his field, the non-specialist for what is happening in every field of medicine. The method for selecting papers for abstracting purposes must be at some time a puzzle for every reader. In his own specialty, he will find papers of such elementary appeal that he wonders why the abstract was ever published. Is it to simplify some aspect of the subject for the general practitioner? On the other hand, the inclusion of occasional abstracts on rare disorders is just as puzzling. Are they to shake our self-esteem on the diagnoses we may have missed, or the treatment of which we were unaware?

The present volume of approximately 750 abstracts represents a triple distillation of medical literature. The editors of the journals in which the papers originally appeared chose them for publication. Next, when the journals were published, a number of papers were selected for printing as abstracts. Of these, Dr. Fabricant again culled the best for inclusion in the first of an annual series of official publications of the J.A.M.A.

Of approximately 750 papers, Internal Medicine is represented by 180, Therapeutics by 150, Surgery by 100, Neurology and Psychiatry by 90, Pediatrics by 60, Gynecology and Obstetrics by 50, Dermatology, Radiology and Urology each by 25, and Anesthesia, Ophthalmology and Laryngology, Pathology and Physiology by 20 or fewer. The lines between the subjects are not finely drawn, and the index is classified only in general terms, so the classifications are not strictly exclusive. But do these numbers represent size and zone of interest, and to whom?

With general grouping, intersections with no subdivisions make for mental acrobatics. Local Treatment with Thorium X for Tuberculosis of the Cervical Lymph Nodes is preceded by Treatment of Diarrhea, and followed by Constitutional Signs of Asthma in Children. Since the abstracts are not grouped sequentially by dates, could they not, in future volumes, be classified by subjects as far as is practical and feasible?

Books of this type are like anthologies. Their purpose is not to please everybody, for the reason that everyone cannot be pleased. The individual specialist will always wonder why space was given to something he is sure is common knowledge, while

the individual general practitioner will sometimes be taken aback by the space given to rare disorders he is certain he will never meet in a lifetime of practice. But each will find something he did not know to be true of his favorite subject, and much of which he was only dimly aware in others. And this lack of continuity may actually be a virtue if it means a frequent browsing. For the price of a moderate-sized steak, this book should be rated as a "best buy."—E.A.B.

CIBA FOUNDATION COLLOQUIA ON ENDOCRINOLOGY. Volume VIII: The Human Adrenal Cortex. G. E. W. Wolstenholme and Margaret Cameron, editors. 265 pages. Illus. Boston: Little, Brown & Co.; London: J. & A. Churchill, 1955. Price, $10.00.

This is another in the series of international symposia sponsored by the Ciba Foundation in London. Although twelve previous small international conferences in this series have covered endocrinologic problems, another was held in the spring of 1954 to discuss hormonal research on the human adrenal cortex. The colloquium was divided into two parts, one concerned largely with histologic and biochemical aspects and corticomedullary relationships, the other dealing with the physiologic and pathologic aspects and with hypothalamic and pituitary relationships. Although mainly concerned with the human adrenal cortex, animal experiments presenting useful supporting information are also included.

Representatives of eight countries participated in the symposium, and the thirty-five papers presented sum up our available information on current research on the adrenals and the fields in which such knowledge may be applied. Two papers are presented on Cushing's syndrome which give adequate coverage to the subject, and three papers cover aldosterone, presenting biologic studies, its biosynthesis in the adrenals, and its clinical and metabolic effects. Other subjects presented include anatomy and histochemistry of the adrenal cortex, cortical zoning, reaction under stress, effect of famine, chromatography of corticosteroids in human blood, metabolic effects of adrenalectomy, sodium retention, to mention only a few.

This volume should have value as a reference book, as it brings together in one place a great deal of previously scattered information, and the discussions which follow each paper should help the reader in evaluating the material presented.—V.E.S.

BÉLA SCHICK AND THE WORLD OF CHILDREN. Antoni Gronowicz. 216 pages, including index. New York: Abelard-Schuman, 1954. Price, $3.75.

It is easy to understand how Antoni Gronowicz spent several years preparing and writing this biography of Béla Schick, for into it he has woven not only the important events in the life of this honored pediatrician but has succeeded in conveying to the reader in a warm-hearted way the simple, shy but friendly, and endearing personality of Dr. Schick. The influence of his early life in a Jewish home at Graz, Austria; the vacations spent with his uncle, a beloved physician, at Bolgar, Austria; the part music played in his life; the long hours of grinding work at little or no salary—these are sympathetically presented to show their effect on the man Béla Schick was to become.

After receiving his medical degree at the Karl Franz University in Graz in 1900, Schick, along with Clemens von Pirquet, became a protégé of Dr. Theodor Escherich, who took them with him as his assistants to the Kinderklinic at the University of Vienna. It was at this clinic in 1902 that these two young men, ages twenty-six and twenty-nine, respectively, began work on the problems of immunity, a task which lasted until 1909. In some strange manner the minds and personalities of these two great men complemented each other and enabled them to make a combined contribution to medicine. Their combined work on immunity led to the

discovery of the von Pirquet test for tuberculosis and the Schick test for immunity to diphtheria in 1913. After discovery of the diphtheria bacillus by Klebs and Löffler and of the diphtheria antitoxin by von Behring, Schick's discovery of the means of depriving the toxin of injurious properties while retaining its antigenic power resulted in the widespread suppression of diphtheria. The First World War prevented wide use of the Schick test in Europe, but in the United States, Dr. William H. Park in 1914 recognized its importance in combating diphtheria, and started a campaign in New York City for its use.

With von Pirquet in 1905, Schick published the first description of serum sickness, which also established the fundamental principles of allergy. Later, with Escherich, he published his famous monograph on scarlet fever, and pronounced the idea that postscarlatinal diseases were allergic in nature. Although Schick had begun work in Vienna in the field of scarlet fever and published a classic monograph on that subject, he later transferred to the study of diphtheria. By 1918 Bela Schick was Professor of Children's Diseases at the University of Vienna, where he was recognized as one of the greatest pediatricians in Europe. His fame had spread to America also, and in 1922 he was invited to become Director of the Pediatrics Department of Mount Sinai Hospital in New York. On September 30, 1923, he arrived in America to begin his distinguished career in many fields in this country. In addition to his duties at Mount Sinai and other hospitals, he became a regular lecturer on the diseases of children at Columbia University. Childhood tuberculosis was also a subject of great interest to him, and one in which he did a large amount of work and in which his diagnostic methods are still basic.

Almost every year, he and his wife traveled to Europe to exchange ideas with European scientists, returning full of ideas to help solve technical and administrative problems in the hospitals, and new therapeutic approaches waiting to be tested.

Winner of the Gold Medal of the New York Academy of Science, the British Addingham Gold Medal, the John Howland Medal of the American Pediatric Society, and one of the founders of the American Academy of Pediatrics, his life and work has always been an inspiration to the younger scientists with whom he came in contact. He was ever alert to seek out talent, to discover, encourage and assist struggling young physicians, helping them obtain scholarships, fellowships and financial assistance so they could continue their work. Always the needs of the children were his first interest, and always was he led by Pasteur's faith that all diseases could be wiped off the face of the earth.

Anyone who has known Dr. Schick will want to have this charming biography of him, and those who know him only by reputation will want to read it for inspiration.—V.E.S.

NEWS OF MEMBERS

Dr. Irvin H. Moore has collaborated with The Borden Company in producing a film entitled "Infant Food Allergy." This picture, which is in sound and color, runs for ten minutes and describes four cases of food allergy with varied symptomatology. It shows the usefulness of the "trial elimination diet" technique in diagnosing food allergy and the value of a hypoallergenic diet in keeping infants symptom-free during the period in which they are particularly susceptible to food allergy.

* * *

Dr. Vincent J. Derbes of New Orleans has recently been appointed Professor of Dermatology at Tulane University School of Medicine.

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IN MEMORIAM

NEWS ITEMS

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*Study of 50 children: Dees, S. C., et al., Ann. Allergy, *11*:297, 1953.

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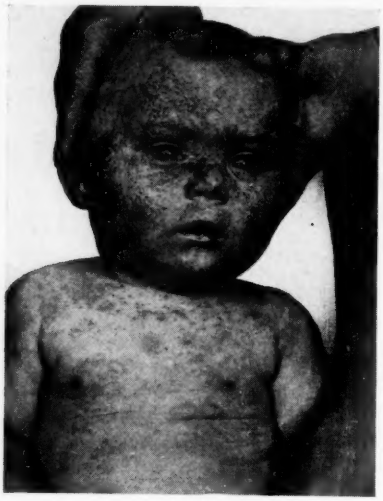
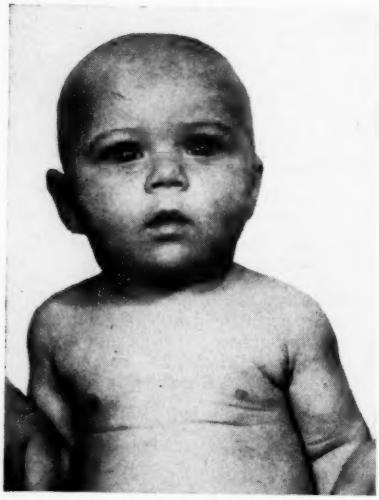


Before Treatment



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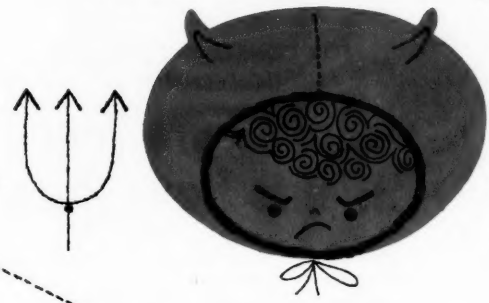

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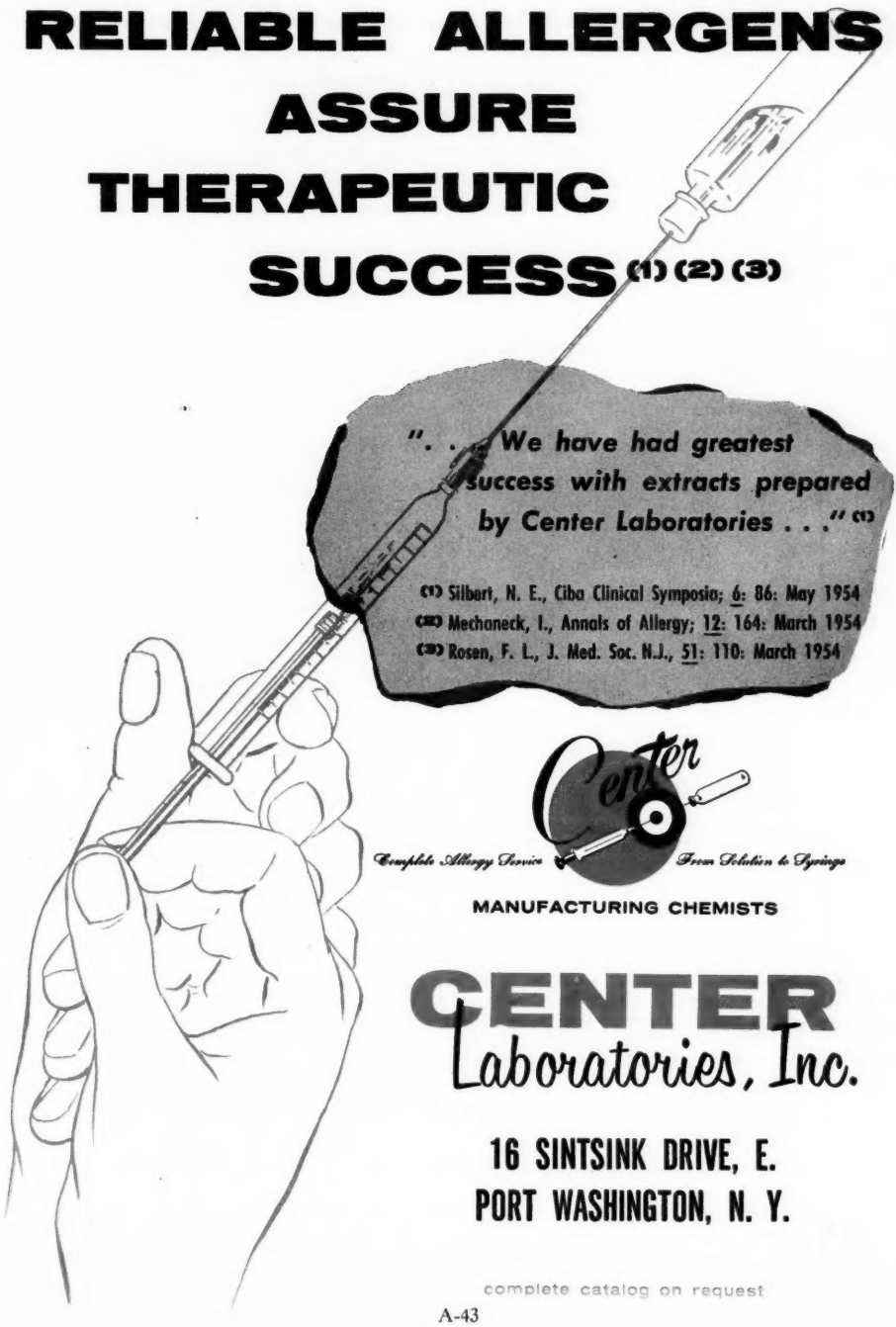

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(1) Silbert, N. E., Ciba Clinical Symposia; 6: 86: May 1954
(2) Mechaneck, I., Annals of Allergy; 12: 164: March 1954
(3) Rosen, F. L., J. Med. Soc. N.J., 51: 110: March 1954

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THE AMERICAN COLLEGE OF ALLERGISTS

Twelfth Annual Instructional Course and Congress
Hotel New Yorker, New York, New York
April 15-20, 1956

The *Twelfth Annual Instructional Course*, April 15-17, 1956, with Dr. Morris A. Kaplan, Chairman, and Dr. M. Murray Peshkin, Co-Chairman, will be held at the Hotel New Yorker in New York. A tentative program has been set up, subject to change. Future issues of the ANNALS OF ALLERGY will contain important announcements and a complete program.

As the Instructional Course is arranged at the present time, Sunday morning, April 15, will be devoted to the basic sciences, and will include an introduction by Dr. M. Murray Peshkin, and lectures on Immunology as Applied to Allergy, Pathology of Allergy and Collagen Diseases, Physiology of Allergy, and Immunochemistry. The afternoon will be devoted to HAY FEVER and Non-seasonal Allergic Rhinitis, and will include discussions on botany and environmental factors. A treatment conference will be held, including such subjects as Specific Immunization, Nonspecific Therapy, Drug Therapy, Surgical Therapy, and Environmental Control. Sunday evening will be given over to a consideration of Office Procedures and a Practical Demonstration.

On Monday morning, April 16, the subject of BRONCHIAL ASTHMA will be covered. The Physiology of Respiration; Classification, Causes, and Complications of Bronchial Asthma; and Differential Diagnosis will be discussed, and a treatment conference will be held covering Specific Therapy, Drug Therapy, Corticosteroid Therapy, and Mechanical and Physical Aids. Between 12:00 and 2:00 there will be a continuation of Office Procedures and Practical Demonstration. Monday afternoon will be devoted to a discussion of ECZEMA AND OTHER ALLERGIC DERMATOSES, and will include such subjects as Pathology of Eczema, Infantile Eczema, Atopic Eczema in Adults, Contact Dermatitis, and Nonatopic Urticarial Dermatoses. A treatment conference will cover Steroid Therapy and Dietary Management. Monday evening will be devoted to an informal banquet where small groups will be able to discuss individual subjects with individual instructors.

The sessions on Tuesday morning, April 17, will cover SPECIAL PROBLEMS IN ALLERGY. The discussions will last for twenty or thirty minutes and will deal with The Importance of the Initial Interview, The Physician-Patient Relationship, Office Management of the Allergic Patient, Prophylaxis of Allergy in Childhood, Life Expectancy in Asthma, Institutional Management of Intractable Asthma in Childhood, and Management of Local and Constitutional Reactions. Between 12:00 and 2:00 Office Procedures and a Practical Demonstration will be conducted. MISCELLANEOUS ALLERGY will be the subject of the afternoon discussions, with special attention to Migraine and Allergic Headache, Urticaria, Allergy in Relation to Hematology, Physical Allergy, Allergy in Relation to the Cardiovascular System, and Psychosomatic Aspects of Allergy. Between 5:00 and 7:00 p.m. Office Procedures and a Practical Demonstration will again be conducted.

The General Scientific Session starts on Wednesday morning, April 18, and papers of fifteen or twenty minutes' length will be presented during the entire day and on Thursday morning, April 19. Between 12:00 and 2:00 the Office Procedures and Practical Demonstration will continue. The annual business meeting will be held on Thursday afternoon at 2:00, followed by the guest speaker who will be introduced by Dr. Giles Koelsche. From 6:00 to 7:30 on Thursday a cocktail party will be held, followed at 8:00 by the annual banquet.

All day Friday, April 20, will be given over to sectional meetings. From 9:00 to 12:00 the sections on Ophthalmic and Otorhinolaryngologic Allergy and on Dermatologic Allergy will meet, and from 12:00 to 2:00 the Ophthalmic and Otorhinolaryngologic Allergy Section will hold a luncheon meeting. From 2:00 to 5:00 p.m. the Sections on Psychosomatic and Pediatric Allergy will meet.

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1. Brown, E. A., and Clancy, R. E.: Presented at the Eleventh Congress of the American College of Allergists, April 29, 1955, Chicago, Illinois. To be published.

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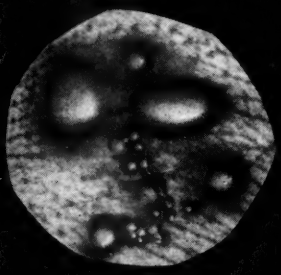

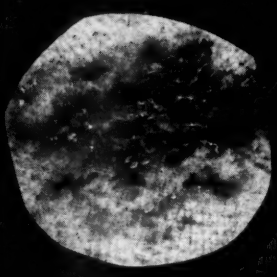

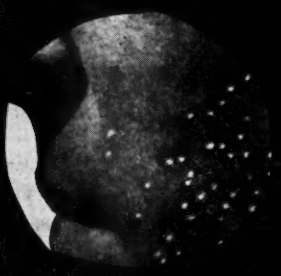

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References: (1) Howles, J. K., Jr.: J. Louisiana M. Soc. 106:54, 1954. (2) Welsh, A. L., and Ede, M.: Ohio M. J., in press. (3) Lincoln, C. S., Jr.: M. Times 83:178, 1955. (4) Arnold, H. L., Jr.: Postgrad. Med., in press. (5) Sigel, H.: Connecticut M. J. 17:912, 1953.

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